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CHEMICAL ABSTRACTS, vol. 97, no. 7, 16th August 1982, page 268, abstract no. 51652z, Columbus, Ohio, US; T. TESHIMA et al.: "A new class of heterocyclic serine protease inhibitors. Inhibition of human leukocyte elastase, porcine pancreatic elastase, cathepsin G, and bovine chymotrypsin A, with substituted benzoxazinones, quinazolines, and anthranilates", & J. BIOL. CHEM. 1982, 257(9), 5085-91

## Description

### Background and Summary of the Invention

- 5 The activity of proteolytic enzymes of the elastase type has been implicated in several pathological conditions, for example in arthritis and in pulmonary emphysema. Pharmacological inhibition of an elastase enzyme would be expected to prevent or ameliorate an associated pathological condition. Trifluoromethyl ketone substituted peptide derivatives which are inhibitors of human leukocytic elastase are described in European Patent Application, Publication number 189305 A2.
- 10 The present invention relates to certain heterocyclic ketones which are human leukocyte elastase (HLE) inhibitors making them useful whenever such inhibition is desired, such as for research tools in pharmacological, diagnostic and related studies and in the treatment of tissue degenerative diseases such as, for example, pulmonary emphysema in mammals. The invention also includes intermediates useful in the synthesis of these heterocyclic ketones, processes for preparing them, pharmaceutical compositions
- 15 containing such heterocyclic ketones and methods for their use.

### Description of the Invention

- According to the invention there are provided compounds of formula I
- 20 (Formula set out on pages following Examples) I wherein the group -Q- is selected from a group consisting of (i) ortho-phenylene, optionally bearing one or two substituents independently selected from a group consisting of halogeno, nitro, an amino group of formula  $-NR^aR^b$ , an acylamino group of formula  $-NHCOR^a$ , hydroxy, an acyloxy group of formula  $-OCOR^a$  (1-4C) alkoxy, (1-4C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-CONR^aR^b$  (including formula  $-CONR^a_2$  when  $R^b = R^a$ ), sulfo, sulfonamido of formula  $SO_2NRR^a$  and (1-3C)hydroxyalkyl; and (ii) a *cis*-vinylene group of formula  $-C(R^a)=C(R^b)-$  wherein
- 25  $R^a$  and  $R^b$  are each independently selected from a group consisting of hydrogen, nitro, an amino group of formula  $-NR^aR^b$ , an acyloxy group of formula  $-OCOR^a$ , (1-4C)alkoxy, (1-6C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-CONR^aR^b$  (including formula  $-CONR^a_2$  when  $R^b = R^a$ ), a hydroxymethyl group, and phenyl optionally bearing one or two substituents chosen from a group consisting of halogeno, nitro, (1-4C)alkoxy, (1-4C)alkyl and trifluoromethyl;
- 30  $R^a$ ,  $R^b$ ,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are each independently selected from a group consisting of hydrogen and (1-4C)alkyl;
- $R^a$  is (1-4C)alkyl;
- 35 X is selected from a group consisting of oxygen and sulfur;
- A is selected from a group consisting of  $-CO-$ ,  $-NH.CO-$  and  $-O.CO-$ ;
- L is selected from a group consisting of phenylene, (1-6C)alkanediy and phenylene(1-3C)alkyl, optionally containing one double bond in the alkyl portion, with the condition that a carbon included in a double bond of an alkenediy or included in an optional double bond of a phenylenealkyl group is not directly bonded to an oxygen or nitrogen atom of group A; and
- 40  $R^1$  is selected from a group consisting of acylsulfonamide of formula  $R^2.S(O_2).NH.CO-$ , acylsulfonamide of formula  $R^2.CO.NH.S(O_2)-$ , Sulfonyleurea of formula  $R^2.NH.CO.NH.S(O_2)-$ , sulfonyleurea of formula  $R^2.S(O_2).NH.CO.NR^3-$ , and trifluoromethylsulfonamide of formula  $CF_3.S(O_2).NH-$  wherein
- $R^2$  is selected from a group consisting of (1-10C)alkyl; trifluoromethyl; (3-10C)cycloalkyl; (6 or 10C)aryl
- 45 optionally substituted by 1 to 3 members of a group consisting of halogeno, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl carboxy, phenyl, and [(1-5C)alkylcarbonyl]amino; and an aromatic heterocyclic group defined as herein below in which up to 3 carbons of the aromatic system may bear a substituent group independently selected from a group consisting of halogeno and trifluoromethyl; and
- $R^3$  is hydrogen or methyl; and
- 50 the pharmaceutically acceptable base-addition salts thereof.
- In this specification, the following definitions are used, unless otherwise described:
- Halogeno is fluoro, chloro, bromo or iodo.
- Aromatic heterocyclic group means a group of from 1 to 15 carbons and from 1 to 4 heteroatoms each of which is independently selected from a group consisting of sulfur, nitrogen and oxygen, and which form 1
- 55 to 3 five- or six-membered rings, at least one of which is aromatic. More particularly, such an aromatic heterocyclic group is a monocyclic or fused bicyclic ring system of from 1 to 10 carbon atoms and from 1 to 4 heteroatoms.
- Alkyl, alkanediy, alkenediy, etc. denote both straight and branched groups.

The radicals R<sup>a</sup>, L and Q may contain chiral centers. The present invention includes compounds of formula I wherein chiral centers included in R<sup>a</sup>, L and Q are of the R and/or S configurations. The radical L may contain a double bond; the present invention includes compounds of formula I wherein a double bond included in L is of the E and/or Z configuration.

5 The compounds of the invention of formula I can be viewed as tripeptidoyl heterocycles. In general, the preferred compounds of the present invention are of the naturally occurring L-amino acid configuration at the chiral centers identified by \* in formula I. The methods of synthesis described below may provide a diastereomeric mixture as a result of the presence of products with both the R and the S configurations at the chiral center identified by # in formula I. While these diastereomers may be separated, it is not  
10 necessary to do so. The preferred compounds are those assigned the S configuration at the chiral center identified by #.

As will be appreciated by those skilled in the art, the activity of the individual isomers is not the same, and it is therefore preferred to utilize the more active isomer. The present invention includes both the diastereomeric mixture and the active S and R isomers.

15 A particular value for an optional substituent on Q when Q is *o*-phenylene, or for an optional substituent on R<sup>a</sup> or R<sup>b</sup> when R<sup>a</sup> or R<sup>b</sup> is phenyl, or for R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> or R<sup>9</sup> when the substituent or group is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, 2-methylpropyl or *t*-butyl. A particular value for an optional substituent on Q when Q is *o*-phenylene, or for R<sup>a</sup> or R<sup>b</sup>, or for an optional substituent on R<sup>2</sup> or R<sup>3</sup> when R<sup>2</sup> or R<sup>3</sup> is phenyl when the substituent or group is (1-4C)alkoxy is, for example, methoxy, ethoxy,  
20 propoxy, isopropoxy, 2-methylpropoxy or *t*-butoxy. A particular value for an optional substituent on Q when Q is *o*-phenylene or for R<sup>a</sup> or R<sup>b</sup> when the substituent or group is [(1-4C)alkoxy]carbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl or *t*-butoxycarbonyl. A particular value for R<sup>a</sup> or R<sup>b</sup>, when it is (1-6C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, 2-methylpropyl, *t*-butyl, pentyl, 3-methylbutyl or hexyl. A particular value for an optional substituent on Q when Q is *o*-phenylene or for an  
25 optional substituent on R<sup>2</sup> or R<sup>3</sup> when R<sup>2</sup> or R<sup>3</sup> is phenyl when the substituent is halogeno is, for example, fluoro, chloro or bromo.

A particular value for a (1-3C)hydroxyalkyl substituent on Q when Q is *o*-phenylene is, for example, hydroxymethyl, 2-hydroxyethyl or 1,1-dimethylhydroxymethyl.

A particular value of R<sup>5</sup> when R<sup>5</sup> is (1-10C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, *t*-butyl  
30 or 4-methylpentyl. A particular value of R<sup>5</sup> when R<sup>5</sup> is (3-10C)cycloalkyl is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, or adamantyl. A particular value for R<sup>5</sup> when R<sup>5</sup> is (6 or 10C)aryl is, for example, phenyl or naphthyl; a particular value for an optional substituent on aryl when the substituent is halogeno is, for example, fluoro, chloro or bromo; and a particular value for an optional substituent on aryl when the substituent is [(1-5C)alkylcarbonyl]amino is, for example, formylamino, acetylamino, 2-methyl-  
35 propanoylamino or 2,2-dimethylpropanoylamino. A particular value for R<sup>5</sup> when R<sup>5</sup> is an aromatic heterocyclic group is, for example, furyl, thienyl, pyridyl or pyrimidinyl; and a particular value for an optional substituent when the substituent is halogeno is, for example, fluoro, chloro or bromo.

A particular value for L when L is phenylene is, for example, *p*-phenylene or *m*-phenylene. A particular  
40 value for L when L is (1-6C)alkanediyl is, for example, methylene, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-2,2-diyl, butan-1,4-diyl, 2-methylpropan-2,3-diyl, 2-methylpropan-1,2-diyl or pentan-1,5-diyl. A particular value for L when L is (2-6C)alkenediyl is, for example, ethen-1,2-diyl, propen-1,2-diyl, propen-1,3-diyl, buten-1,4-diyl, but-2-en-1,4-diyl, penten-1,5-diyl or 3,3-dimethylpropen-1,3-diyl. A particular value for L when L is phenylene(1-3C)alkyl is, for example, *p*-phenylenemethyl, 2-(*p*-phenylene)-  
45 ethyl or 2-(*p*-phenylene)-2-propyl; and when the phenylene(1-3C)alkyl group contains an optional double bond, a particular value for L is, for example 2-(*p*-phenylene)-ethenyl.

A more particular value for an optional substituent on Q when Q is *o*-phenylene is, for example, chloro, dimethylamino, formylamino, hydroxy, acetoxy, methoxy, methyl, trifluoromethyl, carboxy, cyano, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, dimethylaminosulfonyl or hydroxymethyl, including hydroxy, methoxy, carboxy, methoxycarbonyl, aminocar-  
50 bonyl and hydroxymethyl.

A more particular value for R<sup>a</sup> or R<sup>b</sup> is, for example, hydrogen, dimethylamino, acetoxy, methoxy, methyl, trifluoromethyl, cyano, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, hydroxymethyl, phenyl, chlorophenyl, methoxyphenyl, or trifluoromethylphenyl, including hydrogen.

A more particular value for R<sup>4</sup> is R<sup>4</sup>·S(O<sub>2</sub>)·NH·CO·, R<sup>4</sup>·S(O<sub>2</sub>)·NH·CO·NR<sup>2</sup>·, or CF<sub>3</sub>SO<sub>2</sub>NH·.

55 A more particular value for R<sup>5</sup> is, for example, methyl, ethyl, isopropyl, cyclopropyl, cyclopentyl, phenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, 1-naphthyl, 2-thienyl, 2-pyridyl, or chloropyridyl, including methyl, isopropyl, phenyl and 4-chlorophenyl.

A more particular value for R<sup>6</sup> is hydrogen.

A more particular value for A is  $-CO-$ .

A more particular value for L is, for example, *p*-phenylene, ethane-1,2-diyl, ethen-1,2-diyl, *p*-phenylenemethyl or 2-(*p*-phenylene)ethenyl, including *p*-phenylene.

The particular values listed for radicals, substituents and ranges are for illustration only and do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Within the scope of the invention are subgroups, including those in which the heterocyclic ring system containing N, Q and X is:

- (a) a benzoxazole wherein X is oxygen and Q is *o*-phenylene as defined above under (i) in the definition of Q;
- (b) an oxazole wherein X is oxygen and Q is *cis*-vinylene as defined above under (ii) in the definition of Q;
- (c) a benzothiazole wherein X is sulfur and Q is *o*-phenylene as defined above under (i) in the definition of Q; and
- (d) a thiazole wherein X is sulfur and Q is *cis*-vinylene as defined above under (ii) in the definition of Q.

A value of X in formula I of particular interest is oxygen. Values for  $R^4$ , L.A- in formula I of particular interest include for  $R^4$ :  $R^5$ ,  $S(O_2)-NH.CO-$  and  $R^5$ ,  $S(O_2).NH.CO.NR^6-$ , especially  $R^5$ ,  $S(O_2)-NH.CO-$ , for L: *p*-phenylene; and for A:  $-CO-$ . A value for  $R^6$  of particular interest is 4-chlorophenyl.

Specific compounds of formula I are described in the accompanying Examples. Compounds which are preferred include:

- (i) 4-[(4-Chlorophenyl)sulfonylamino]carbonyl]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide;
- (ii) 4-[(4-Chlorophenyl)sulfonylamino]carbonyl]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide; and
- (iii) 4-[(4-Chlorophenyl)sulfonylamino]carbonyl]benzoyl]-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide.

The salts of the compounds of formula I include pharmaceutically acceptable base-addition salts such as those derived from alkali metal hydroxides such as sodium hydroxide, alkali metal carbonates and bicarbonates, alkaline earth hydroxides and organic amines. Such salts may be prepared by dissolving the heterocyclic ketone in a mixture of water and a water-miscible organic solvent, adding an aqueous solution of the base and recovering the salt from the aqueous solution.

The compounds of formula I may be made by processes which include processes known in the chemical art for the production of structurally analogous heterocyclic and peptidic compounds. Such processes for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as defined above (and a radical of formula Q may include a protecting group):

- (A) For a compound of formula I, oxidizing a corresponding alcohol of formula III:  
(Formula set out on pages following Examples) III Methods which are useful include the use of oxalylchloride, dimethyl sulfoxide, and a tertiary amine (see Marx, M. et al., *J. Org. Chem.*, **49**, 788-793 (1984)); the use of acetic anhydride and dimethyl sulfoxide; the use of dimethyl sulfoxide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and dichloroacetic acid in, for example, toluene (see, e.g. Example 19); the use of chromium trioxide pyridine complex in methylene chloride; and the use of Dess-Martin periodinane [1,1,1-triacetoxy-2,1-benzoxiodol-3(H)-one] (method of Dess, D. B. et al., *J. Org. Chem.*, **48**, 4155-56 (1983)). When Q has the value (i) *ortho*-phenylene and X is oxygen, generally a preferred oxidant is Dess-Martin periodinane; however, when Q bears an aminocarbonyl group, the use of chromium trioxide pyridine complex or of dimethyl sulfoxide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and dichloroacetic acid is preferred. When an alcohol of formula III contains a basic nitrogen, it is generally preferable to use an alternative method or to protect the basic nitrogen before oxidation and deprotect it after oxidation to provide the corresponding compound of formula I.
- (B) For a compound of formula I wherein  $R^4$  has the value  $R^5$ ,  $S(O_2).NH.CO-$ , reacting a corresponding compound of formula IV

(Formula set out in pages following Examples) IV wherein  $R^7$  is carboxy (which compound is hereinafter referred to as "acid of formula IV") with a sulfonamide derivative of formula  $R^5$ ,  $SO_2.NH_2$  in the presence of a dehydrating agent or reacting a reactive derivative of an acid of formula IV with a sulfonamide, or a salt thereof, of formula  $R^5$ ,  $SO_2.NH_2$ . Thus, for example, a free acid of formula IV may be reacted with a suitable dehydrating agent, for example, with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or with a hydrochloride or hydrobromide salt thereof, optionally together with an organic base, for example, 4-dimethylaminopyridine, and with a sulfonamide of

formula  $R^5.SO_2.NH_2$  in the presence of a suitable solvent or diluent, for example, dichloromethane, at a temperature in the range of, for example, 0 to  $50^\circ C$ ; but preferably at or near ambient temperature.

Alternatively, a reactive derivative of an acid of formula IV, for example, an acid halide (such as the acid chloride), acid anhydride or a mixed acid anhydride (such as that formed from N,N-diphenylcarbamoylcarbamoylpyridinium chloride), may be reacted with an alkali metal salt (such as the lithium, sodium or potassium salt) of the appropriate sulfonamide of formula  $R^5.SO_2.NH_2$ , conveniently at or near ambient temperature and in a suitable solvent or diluent, for example, tetrahydrofuran, N,N-dimethylformamide or dichloromethane.

(C) For a compound of formula I wherein  $R^4$  has the value  $R^5.CO.NH.S(O_2)-$ , reacting a corresponding compound of formula IV in which  $R^7$  has the value  $H_2N.S(O_2)-$  with an acid of formula  $R^5.COOH$  using a similar method to one of those described above in part (B).

(D) For a compound of formula I wherein  $R^4$  has the value  $R^5.NH.CO.NH.S(O_2)-$ , reacting a corresponding compound of formula IV in which  $R^7$  has the value  $H_2N.S(O_2)-$  with an isocyanate of formula  $R^5.NCO$ . For example, an intermediate of formula IV in which  $R^7$  is  $H_2N.S(O_2)-$  may be treated with phenylisocyanate to provide a corresponding product of formula I in which  $R^5$  is phenyl.

(E) For a compound of formula I wherein  $R^4$  has the value  $R^5.S(O_2).NH.CO.NR^6-$ , reacting a corresponding compound of formula IV in which  $R^7$  has the value  $HNR^6-$  with a sulfonylisocyanate of formula  $R^5.S(O_2).NCO$ ; or alternatively, for a compound in which  $R^6$  has the value H, reacting a corresponding compound of formula IV in which  $R^7$  has the value  $-NCO$  with a sulfonamide of formula  $R^5.S(O_2).NH_2$ . The reaction may be carried out, for example, at room temperature in a suitable inert organic solvent such as tetrahydrofuran or dichloromethane.

(F) For a compound of formula I wherein  $R^4$  has the value  $CF_3.S(O_2).NH-$ , reacting a corresponding amine of formula IV in which  $R^7$  has the value  $H_2N$  with trifluoromethanesulfonic anhydride, for example, at  $0^\circ$  in an inert solvent such as dichloromethane.

(G) For a compound of formula I wherein A has the value  $-CO-$ , coupling an acid of formula  $R^4-L-COOH$  (or a reactive derivative thereof) with an amino ketone of formula V:

(Formula set out on pages following Examples) V For example, the coupling may be carried out using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4-dimethylaminopyridine or 1-hydroxybenzotriazole in an inert solvent such as tetrahydrofuran. Similarly, a compound of formula I wherein A has the value  $-NH.CO-$  or  $-O.CO-$  may be prepared from a corresponding amino ketone of formula V using a similar method to one described below for the preparation of a starting material alcohol of formula III from an amino alcohol of formula XV.

It may be desired to optionally use a protecting group during all or portions of the above described processes; the protecting group then may be removed when the final compound or a required starting material is to be formed, for example, as described in Examples 5 and 7.

Whereafter, modifying a functional group of a compound of formula I by a conventional method to afford a different compound of formula I, such as, for example, converting an optional carboxy or alkoxy carbonyl substituent on Q to an aminoacyl substituent, may be carried out.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt is required, it may be obtained by reaction of the acidic form of a compound of formula I with a base comprised of a physiologically acceptable cation and a physiologically acceptable anion and affording a physiologically acceptable cation or by any other conventional procedure.

If not commercially available, the necessary starting materials for the above procedures may be made by procedures which are selected from standard techniques of heterocyclic chemistry and peptide chemistry, techniques which are analogous to the synthesis of known, structurally similar compounds, and techniques which are analogous to the above described procedures or the procedures described in the Examples.

As will be clear to one skilled in the art, a variety of sequences is available for preparation of the starting materials. According to one of the available routes, a key intermediate of formula XI may be prepared as shown in Scheme 1 (set out on pages following Examples) beginning with valinol (formula VII) and utilizing the intermediates of formulae VIII, IX and X as described in Example 1. Alternatively valinol (formula VII) may be coupled with an acid of formula IX to afford an alcohol of formula XII; and an alcohol of formula XII may be oxidized to provide an aldehyde of formula XI as a key intermediate.

As shown in Scheme II (set out on pages following Examples) an intermediate aldehyde of formula XI may be converted into a starting material alcohol of formula III, a starting material ketone of formula IV or a starting material amino ketone of formula V.

An aldehyde of formula XI may be reacted with, for example, an alkali metal cyanide, such as, for example, sodium cyanide or potassium cyanide, to form a cyanohydrin of formula XIII wherein W is CN. More preferably, an aldehyde of formula XI may be converted into a cyanohydrin of formula XIII wherein W is CN by treatment with acetone cyanohydrin, for example as described in Example 4a. In addition trimethylsilylcyanide may be used for the transformation, the trimethylsilyl group being removed upon acidic workup. The hydroxy group of such a cyanohydrin may optionally be protected by, for example, an acetyl group or a trimethylsilyl or t-butyldimethylsilyl group.

A cyanohydrin of formula XIII wherein W is CN may be converted into a corresponding heterocyclic alcohol of formula XIV, either directly or via an isolated intermediate using a conventional method. For example, conversion of a compound of formula XIII wherein W is CN into a corresponding compound of formula XIV wherein Q has the value *o*-phenylene as defined above may be carried out using a similar procedure to one described in Hölljes, E. L. and Wagner, E. C., *J. Org. Chem.*, (1944), 9, 31. Conversion of a compound of formula XIII wherein W is CN into a corresponding compound of formula XIV wherein Q has the value *cis*-vinylene as defined above may be carried out using a similar procedure to one described in Lora-Tamato, M. et al. *Chem. Ber.*, (1964), 97, 2230, 2234 or in Kitatani, K. et al. *Tet. Lett.*, (1974), 1531.

Alternatively, a cyanohydrin of formula XIII wherein W is CN may be transformed into an imide of formula XIII where W is -C(NH)OR and R is, for example, methyl or ethyl, preferably as its, for example, hydrochloride salt. An imide of formula XIII wherein W is -C(NH)OR may be transformed into a corresponding heterocyclic alcohol of formula XIV; the intermediate imide may be optionally isolated. The chemistry of imides has been reviewed in "The Chemistry of Amides and Imides," Saul Patai, Ed., John Wiley and Sons, N.Y., 1975, p. 385 and in Roger, R. and Nielson, D. G., *Chem. Rev.*, (1981), 81, 1979. Conversion of an imide of formula XIII wherein W is -C(NH)OR into a corresponding compound of formula XIV wherein Q has the value *o*-phenylene as defined above under (i) in the definition of Q may be carried out using a similar procedure to one described in King, F. E. and Acheson, R. M., *J. Chem. Soc.*, (1949), 1396; or in Reid, W. et al. *Liebigs Ann. Chem.*, (1964), 676, 114. Conversion of a compound of formula XIII wherein W is -C(NH)OR into a corresponding compound of formula XIV wherein Q has the value *cis*-vinylene as defined above under (ii) in the definition of Q and X is oxygen may be carried out using a similar procedure to one described in Wiley, R.H., *Chem. Rev.*, (1945), 37, 401; or in Cornforth, J. W., and Cornforth, R. H., *J. Chem. Soc.*, (1947), 96; (1953), 93.

As a further alternative, an imide of formula XIII wherein W is -C(NH)OR may be hydrolyzed to the corresponding ester of formula XIII wherein W is -COOR. By using an ester of formula XIII wherein W is -COOR, a corresponding acid of formula XIII wherein W is -COOH (available by hydrolysis of the ester in a conventional manner), or a different activated derivative of an acid of formula XIII wherein W is COOH, and a conventional method, a corresponding compound of formula XIV may be prepared. For example, for a compound of formula XIV wherein Q is *o*-phenylene as defined above under (i) in the definition of Q, a similar method to one described in Landenberg, A., *Chem. Ber.*, (1876), 9, 1524; in Galats, L. C., *J. Amer. Chem. Soc.*, (1948), 70, 1967; in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., J. Wiley & Sons, N.Y., 1957, p. 421; in Lankeza, H. P. and Knaut, A. E., *J. Amer. Chem. Soc.*, (1931), 53, 309 and 1959; in Lankeza, H. P. and Vopicka, E., *ibid.*, (1936), 58, 609; or in "The Chemistry of Heterocyclic Compounds," P. N. Preston, Ed., (1981), 40, 6-12 may be used. For example, for a compound of formula XIV wherein Q is *cis*-vinylene as defined above under (ii) in the definition of Q and X is oxygen, a similar method to one described in Wasserman, H. H. and Lu, T.-J., *Tet. Lett.*, (1982), 3831; in Davidson, D. et al. *J. Org. Chem.*, (1937), 2, 328; or in Weigand, E. E. and Rathburn, D. W., *Synthesis*, (1970) 648 and *J. Chem. Eng. Data*, (1973), 18, 237 may be used. For example, for a compound of formula XIV wherein Q is *cis*-vinylene as defined above under (ii) in the definition of Q and X is sulfur, a similar method to one described in Gabriel, S., *Chem. Ber.*, (1910), 43, 134 and 1283; in Bachstet, M., *ibid.* (1947), 47, 3163; or in Wiley, R. H. et al. *Org. Reactions*, (1951), 6, 367 may be used.

Another alternative for the preparation of certain compounds of formula XIV wherein X is sulfur is the use of a thioamide of formula XIII wherein W is -CSNH<sub>2</sub>. A thioamide of formula XIII wherein W is -CSNH<sub>2</sub> may be obtained, for example, from a corresponding nitrile in a conventional manner, such as, for example, treatment with hydrogen sulfide, optionally employing a basic catalyst, such as, for example, triethylamine. Thus, for example, a thioamide of formula XIII wherein W is -CSNH<sub>2</sub> may be converted into a corresponding compound of formula XIV wherein Q is *cis*-vinylene as defined above under (ii) in the definition of Q and X is sulfur by using a similar method to one described in Schmidt, V. et al. *Synthesis*, (1966), 992 or in Wiley, R. H. et al. *Org. Reactions*, (1957), 6, 367 and 378.

A different route from an aldehyde of formula XI to a heterocyclic alcohol of formula XIV involves the use of a preformed heterocyclic reagent. For example, an organolithium reagent of formula XVI wherein Y is lithium may be reacted directly with an aldehyde of formula XI to provide a corresponding alcohol of

formula XIV. When X is oxygen, it may be preferred or necessary to use a different method. Reagents of formula XVI wherein Y is lithium may be prepared and used as described, for example, in Wasserman, H. H. et al. *Tet. Lett.*, (1981), 22, 1737; in Schroeder, R. et al. *Liebigs Ann. Chem.*, (1975), 533; in Beraud, J. and Metzger, J., *Bull. Soc. Chem. France*, (1962), 2072; in Shiriet, D. A. and Alley, P. W., *J. Amer. Chem. Soc.*, (1957), 79, 4922; in Ogura, H. and Takahashi, H., *J. Org. Chem.*, (1974), 39, 1374; in Justin, P. and Hoffmann, H. J., *Chem. Ber.*, (1973), 106, 594; and in Justi, P. and Sakriss, W., *ibid.*, (1973), 106, 2815.

Alternatively, for example, a 2-trimethylsilyl heterocyclic reagent of formula XVI wherein Y is trimethylsilyl may be condensed with an aldehyde of formula XI to provide an intermediate o-trimethylsilyl derivative of a corresponding alcohol of formula XIV. The alcohol of formula XIV may then be obtained by removal of the trimethylsilyl group using a conventional procedure. Reagents of formula XVI wherein Y is trimethylsilyl may be prepared and used in a manner similar to those described, for example, for 4-methyl-2-trimethylsilyloxazole, 2-trimethylsilylbenzothiazole and 2-trimethylsilylthiazole in A. Dondoni, et al. *Tet. Lett.*, (1985), 26, 5477; in A. Dondoni et al., *J. Chem. Soc., Chem. Commun.*, (1984), 258; and in A. Medici et al. *Tet. Lett.*, (1983), 24, 2901.

By using a procedure similar to one described in Levin, J. I. and Weinreb, S. M., *J. Org. Chem.*, (1984), 49, 4325, an oxazole of formula XIV wherein X is oxygen and Q is cis-vinylene as defined above under (ii) in the definition of Q may be prepared from a corresponding oxazoline (4,5-dihydrooxazole). The oxazoline may be prepared, for example, in a conventional manner from a corresponding intermediate of formula XIII wherein W is CN, -C(NH)OR, -COOR, or -COOH, or by reaction of an appropriate organometallic reagent with a corresponding compound of formula XI. Thiazolines may similarly be prepared and dehydrogenated to afford thiazoles of formula XIV wherein X is sulfur and Q is cis-vinylene as defined under (ii) in the definition of Q.)

An alcohol of formula XIV may be converted into a corresponding amino alcohol of formula XV by removal of the CBZ-group using a conventional method, such as for example, hydrogenolysis over a palladium on carbon catalyst at about 3 bars pressure and ambient temperature in an appropriate solvent such as, for example, ethanol.

An amino alcohol of formula XV may be converted into a starting material of formula III by reacting the amino alcohol of formula XV with an appropriate acylating agent. For example, when A is -CO-, appropriate acylating agents are activated derivatives of acids of formula R<sup>4</sup>.L.COOH, for example, activated derivatives thereof generated in situ when using conventional coupling reagents, such as, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole or 4-dimethylaminopyridine, as well as, for example, acid chlorides of formula R<sup>4</sup>.L.COCl. When A is -NH.CO-, appropriate acylating agents include isocyanates of formula R<sup>4</sup>.L.NCO. When A is -O.CO-, appropriate acylating agents include chloroformates of formula R<sup>4</sup>.O.CO.Cl. In general, the acylation is performed in an inert diluent or solvent, such as dichloromethane, tetrahydrofuran or dioxane, and at a temperature in the range of, for example, 0-80°. An organic or inorganic base such as triethylamine, 4-methylmorpholine, 4-dimethylaminopyridine, potassium carbonate or sodium hydroxide may also conveniently be used as an acid acceptor when appropriate.

Starting material ketones of formula IV may also be obtained from an intermediate alcohol of formula XV as shown in Scheme II. Thus, for example, for a starting material of formula IV wherein R<sup>1</sup> has a value of R<sup>3</sup>O<sub>2</sub>C-, H<sub>2</sub>N.SO<sub>2</sub>-, or R<sup>4</sup>NH- and R<sup>2</sup> has a value defined below, an amino alcohol of formula XV may be converted into a corresponding alcohol of formula XVII by using a method analogous to one described above for preparation of a compound of formula III and an analogous reagent, such as, for example R<sup>7</sup>.L.COOH, R<sup>7</sup>.L.COCl, R<sup>7</sup>.L.NCO or R<sup>7</sup>.LO.COCl. Then, by using a similar oxidation process to one described in process (A), an alcohol of formula XVII may be oxidized to provide a starting material ketone of formula IV. A starting material ketone of formula IV wherein R<sup>1</sup> has a value of -NCO may be prepared from a corresponding ketone of formula IV wherein R<sup>1</sup> is carboxy by use of a modified Curtius reaction using, for example, diphenylphosphorylazide and triethylamine in benzene or toluene at 80° (See T. Shiomi, K. Ninomiya and S. Yamada, *J. Amer. Chem. Soc.*, (1972), 94, 6203). A starting material of formula IV wherein R<sup>1</sup> has the value carboxy may be prepared by decomposing a suitable, corresponding ester of formula IV wherein R<sup>1</sup> has the value R<sup>3</sup>O<sub>2</sub>C- in which R<sup>2</sup> is a conveniently removed acid protecting group, for example, phenyl, benzyl, or (1-6C)alkyl optionally bearing an acetoxy, (1-4C)alkoxy or (1-4C)alkylthio substituent.

A particular value for R<sup>2</sup> is, for example, methyl, ethyl, propyl, t-butyl, acetoxymethyl, methoxymethyl, 2-methoxyethyl, methylthiomethyl, phenyl, or benzyl.

It will be appreciated that the decomposition of an ester of formula IV wherein R<sup>1</sup> is R<sup>3</sup>O<sub>2</sub>C- can be performed using any one of a variety of procedures well known in the art of organic chemistry. Thus, it may be carried out, for example, by conventional hydrolysis under acid or base conditions, adjusted as necessary to minimize any hydrolytic removal of other functional groups in the molecule. Alternatively, in



certain circumstances, for example, when  $R^2$  is *t*-butyl, it may be preferred to carry out the decomposition using acid catalysis, for example, by treating an ester of formula IV with, for example, trifluoroacetic acid at a temperature of, for example, 0-40 °C, in a suitable solvent or diluent such as dichloromethane. In addition, when  $R^2$  is *t*-butyl, the decomposition may be performed, for example, by using trimethylsilyl triflate and then water, in a conventional manner. Still further, in certain circumstances, for example, when  $R^2$  is benzyl, it may be possible to carry out the decomposition by reductive means, for example, by the use of hydrogen at a pressure of about three bars in the presence of a suitable catalyst, such as palladium or platinum, conveniently on charcoal as a support.

Starting material amino ketones of formula V may be obtained from corresponding alcohols of formula XIV via the corresponding ketones of formula VI. Thus, by using an oxidation procedure similar to one described above in method (A), an alcohol of formula XIV may be oxidized to a corresponding ketone of formula VI, for example, as described in [Example 7d](#) and [Example 8b](#). Removal of the *N*-protecting group from a ketone of formula VI will then provide a corresponding starting material amino ketone of formula V. The protecting group conveniently may be removed using, for example, trifluoromethanesulfonic acid in dichloromethane at room temperature. It is convenient to isolate an amino ketone of formula V so prepared as its crude trifluoromethanesulfonic acid salt and use it directly for the preparation of a corresponding product of formula I, for example, as described in [Example 7f](#). If an amino ketone of formula V is isolated in the form of its free base, for example as described in [Example 8c](#), it is preferable to use the material at once because of the limited stability of the free base.

Starting material ketones of formula IV may also be prepared from corresponding amino ketones of formula V using analogous methods to those described above for the preparation of alcohols of formula XVII from corresponding alcohols of formula XV.

An alternative, analogous approach to the starting materials of formulae III, IV and V is outlined in Scheme III (set out on pages following Examples). A protected valinal, for example CBZ-valinal, may be converted into a corresponding protected heterocyclic alcohol of formula XIVa by using a method analogous to one described above for the conversion of a protected aldehyde of formula XI into a protected heterocyclic alcohol of formula XIV. The conversion may be carried out stepwise through analogous intermediates of formula XIIIa or directly by using a heterocyclic reagent of formula XVI. An alcohol of formula XIVa may be deprotected to provide an amino alcohol of formula XVa. By coupling with an acid of formula IXa, an amino alcohol of formula XVa may be converted into an alcohol of formula XIV to be used as described in Scheme II. Alternatively, an amine of formula XVa may be coupled with an acid of formula IXa (prepared by using standard methods or methods analogous to those described above) to provide a starting material of formula III, for example, as described in [Example 19](#). In addition, an amine of formula XVa may be coupled with an acid of formula IXb (prepared by using standard methods or methods analogous to those described above) to provide a compound of formula XVII, which may be converted into a starting material of formula IV.

A further approach to starting materials of formulae IV and V, as well as to compounds of formula I, also involves the use of organometallic reagents of formula XVI wherein Y is lithium, especially when X is sulfur, as illustrated in Scheme IV and [Example 13](#) and [Example 14](#). Thus, for example, a suitably amino-protected, *N,N*-disubstituted valinamide, such as benzyloxycarbonyl protected, *N*-methoxy-*N*-methylvalinamide of formula XX, may be treated with a lithiated heterocycle, such as 2-lithiothiazole or 2-lithiobenzothiazole, to afford a corresponding ketone of formula XXI. Removal of the amino-protecting group from a compound of formula XXI by a conventional method affords a corresponding aminoketone of formula XXII. By coupling an acid of formula IX with an amine of formula XXII, a corresponding ketone of formula VI may be obtained. As described above, a ketone of formula VI may be converted into a starting material of formula V, which starting material of formula V may be further converted into a starting material of formula IV. By coupling an acid of formula IXa with an amino of formula XXII, a corresponding product of formula I may be obtained. Similarly, by coupling an acid of formula IXb with an amino of formula XII a corresponding starting material of formula IV may be obtained directly. Also, by use of analogous methodology to that described for the conversion of an amide of formula XX, into an amino ketone of formula XXII, other intermediate compounds, such as those of formula XXIII, formula V and formula IV wherein  $R^2$  is  $\text{HNHR}^3$ , may be obtained.

As will be clear to one skilled in the art, the order of steps in the sequences leading to the starting materials and products of the invention may be altered if appropriate considerations relative to coupling methods, racemization, deprotection methods, etc. are followed.

Inhibition Measurements:

The potency of compounds of the invention to act as elastase inhibitors is initially determined by the ability of a compound of the invention to inhibit the action of human leukocyte elastase (HLE) on a low molecular weight peptide substrate. The potency of an inhibitor is evaluated by obtaining a kinetic determination of the dissociation constant,  $K_i$ , of the complex formed from the interaction of the inhibitor with HLE. The substrate used was the anilide methoxysuccinyl-alanyl-alanyl-prolyl-valine-p-nitroanilide as described by Nakajima, K. et al. in *J. Biol. Chem.*, 245, 4027-4032 (1979) and by Teshima, T. et al. in *J. Biol. Chem.*, 257, No. 9, 5085-5091 (1982). The HLE enzyme used in these studies may be obtained from Elastin Products of St. Louis, Missouri or can be purified according to Viscarello, B. R. et al. in *Preparative Biochemistry*, Vol. 13, pages 57-67, (1983) as also described in European Patent Application, Publication number 189305 A2. From the thus purified HLE, a standard rate of production of p-nitroaniline was measured at 25°C spectrophotometrically in the visible spectrum at 410 nanometers with automatic data acquisition from a Cary 210 spectrophotometer obtained from Varian Associates. Reactions were initiated by injection of 10 microliters of the HLE solution into a 3 milliliter cuvette containing 2.89 milliliters of buffer (10 millimolar sodium phosphate, 500 millimolar NaCl, pH 7.6), 50 microliters substrate solution in DMSO, and 50 microliters of DMSO. Initial, steady-state reaction velocities of p-nitroaniline production were calculated by a fit of the experimental data to a linear dependence on time by linear least squares. This velocity, determined with no inhibitor present, was used as a standard in the calculation of inhibitor  $K_i$  values.

In general, the heterocyclic ketones of the present invention are not "slow-binding" inhibitors of HLE; however, if the heterocyclic ketones are found to be "slow-binding" inhibitors of HLE, special methods of analysis to accurately determine  $K_i$  values for their inhibition of HLE are carried out. (See Williams, J. W. and Morrison, J. F., *Meth. Enz.* 63, 437 (1979) for a description of these methods.) In a typical experiment, 2.89 ml of buffer (10 millimolar sodium phosphate, 500 millimolar sodium chloride, pH 7.6), 50 microliters of inhibitor solution in DMSO, and 50 microliters of substrate solution in DMSO are added to a 3 milliliter cuvette. The cuvette is stoppered, inverted several times to mix its contents and maintained at (25°C) in the spectrophotometer. After a period of five minutes to allow the reaction solution to come to thermal equilibrium, 10 microliters of stock enzyme solution are added to the cuvette to initiate the reaction. Duplicate or triplicate runs are done at zero inhibitor concentration and at least three non-zero inhibitor concentrations.  $K_i$  values are calculated according to methods outlined in the above reference by Williams and Morrison. The  $K_i$  values for selected compounds are less than  $10^{-7}$ M. For example, the  $K_i$  value for the compound of Example 1 is  $3.3 \times 10^{-10}$ M.

35 Animal Models

Animal models of emphysema include intratracheal (i.t.) administration of an elastolytic protease to cause a slowly progressive, destructive lesion of the lung. These lesions are normally evaluated a few weeks to a few months after the initial insult. However, these proteases also induce a lesion that is evident in the first few hours. The early lesion is first hemorrhagic, progresses to an inflammatory lesion by the end of the first 24 hours and resolves in the first week post insult. To take advantage of this early lesion, the following model was used.

Hamsters are first lightly anesthetized with Brevital. Phosphate buffered saline (PBS) pH 7.4, either alone or containing 400 µg of human leukocyte elastase (HLE), is then administered directly into the trachea. Twenty-four hours later the animals are killed and the lungs removed and carefully trimmed of extraneous tissue. Following determination of wet lung weight, the lungs are lavaged with PBS and total lavagable red and white cells recovered are determined. The values for wet lung weights, total lavagable red cells and total lavagable white cells are elevated in a dose-dependent manner following administration of HLE. Compounds that are effective elastase inhibitors can prevent or diminish the severity of the enzyme-induced lesion resulting in lower wet lung weight and reduced values for total lavagable cells, both red and white, relative to administration of HLE alone. Compounds can be evaluated by administering them either with or at various times prior to administration of HLE to determine their utility in preventing an HLE lesion. Compounds of this invention produced statistically significant reductions in wet lung weight and total lavagable cells relative to HLE alone.

Compounds of the present invention which were tested exhibited activity in at least one of the tests described above under Inhibition Measurement or Animal Model. It should be noted that there are not always a direct correlation between the activities of the compounds measured as  $K_i$  values in the Inhibition Measurement test and the reduced values for total lavagable cells and wet lung weights relative to the

administration of HLE alone obtained in the Animal Model test. In general, no overt signs of acute toxicity were noted for compounds of the present invention tested in the Animal Model.

The compounds of the present invention may be administered to a warm-blooded animal in need thereof for treatment of a tissue degenerative disease, particularly a human, in particular for the treatment of emphysema. The preferred mode of administration may be via a powdered or liquid aerosol. In a powdered aerosol, compounds of the invention may be administered in the same manner as cromolyn sodium via a "Spinhaler" (a trademark) turbo-inhaler device obtained from Fisons Corp. of Bedford, Massachusetts at a rate of about 0.1 to 50 mg per capsule, 1 to 8 capsules being administered daily for an average human. Each capsule to be used in the turbo-inhaler contains the required amount of a compound of the invention with the remainder of the 20 mg capsule being a pharmaceutically acceptable carrier such as lactose. In a liquid aerosol, the compounds of the invention are administered at the rate of about 100 to 1000 micrograms per "puff" or activated release of a standard volume of propellant. The liquid aerosol would be given at the rate of 1 to 8 puffs per day with variation in dosages due to the severity of the conditions being treated, the weight of the patient and the particular size distribution of the aerosol since smaller particles will achieve greater lung penetration. Propellants, e.g., a fluorinated hydrocarbon or isobutane, containers, valves and actuators for liquid aerosols are described by L. Lachman et al. in "The Theory and Practice of Industrial Pharmacy," Lea and Febiger, Philadelphia (1976).

Alternatively, the mode of administration may be oral or parenteral, including subcutaneous deposit by means of an osmotic pump. The compounds of the invention may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg per unit of dosage with conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, e.g. as described in U.S. Patent No. 3,755,340. For parenteral administration, a 1 to 10 ml intravenous, intramuscular or subcutaneous injection would be given containing about 0.02 mg to 10 mg/kg of body weight of a compound of the invention 3 or 4 times daily. The injection would contain a compound of the invention in an aqueous isotonic sterile solution or suspension optionally with a preservative such as phenol or a solubilizing agent such as ethylenediaminetetraacetic acid (EDTA).

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°;
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°;
- (iii) flash chromatography was carried out on Merck Kieselgel (Art 9385) [obtained from E. Merck, Darmstadt, W. Germany]; if "acidic silica gel" is indicated, material custom prepared by J. T. Baker Chemical Co., Phillipsburg, NJ, USA, and having a pH of about 6 when slurried in water was used; thin layer chromatography (TLC) was carried out on Analtech 0.25 mm silica gel GHLF plates (Art 21521), obtainable from Analtech, Newark, DE, USA;
- (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) melting points are uncorrected and (d) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- (vi) all final products were essentially pure by TLC and had satisfactory nuclear magnetic resonance (NMR) spectra and microanalytical data;
- (vii) yields are given for illustration only and are not necessarily those which may be obtained by diligent process development; preparations were repeated if more material was required;
- (viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 80 MHz or 250 MHz using CDCl<sub>3</sub>, DMSO-d<sub>6</sub> or CD<sub>3</sub>OD as solvent; conventional abbreviations for signal shape are used, for example: s, singlet; d, doublet; m, multiplet; br, broad; etc; in addition "Ar" signifies an aromatic group or signal;
- (ix) reduced pressures are given as absolute pressures in pascals (Pa); other pressures are given as gauge pressures in bars;
- (x) chemical symbols have their usual meanings; the following abbreviations have also been used: min (minutes), hr (hours), v (volume), w (weight); mp (melting point), l [liter(s)], ml (milliliter(s)), g [gram(s)], mg (milligram(s));
- (xi) solvent ratios are given in volume: volume (v/v) terms; ratios of solids are given in weight:weight (w/w) terms;

(xii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionization mode using a direct exposure probe; when given, only peaks ten percent of the base peak and larger are reported; and

(xiii) when high pressure liquid chromatography (HPLC) data is reported,  $t_R$  (retention time) is given min, FR (flow rate) is given in ml/min, Col A is a 'Zorbax' (a trademark) ODS analytical column (4.6 mm x 25 cm) and Col B is a 'Phenomenex' (a trademark) 'Zorbax' C-8 analytical column (4.6 mm x 35 cm). NOMENCLATURE: For uniformity and clarity, "amino acid sequence" type names are used whenever possible. In general, a stereochemical identification of a chiral center as (S) indicates that the product is estimated to contain at least 95% of the (S)-isomer at the center indicated; the absence of an identification of stereochemistry at a chiral center indicates a mixture of isomers which is not necessarily 1:1 at the center indicated.

#### Example 1

(S)-[4-{(4-Chlorophenyl)sulfonylaminocarbonyl}benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q-2-benzoxazolyl, A=CO, L=p-phenylene,  $R^4=R^5$ .S(O<sub>2</sub>).NH.CO-,  $R^5$ =4-ClC<sub>6</sub>H<sub>4</sub>).

#### a. N-Benzoyloxycarbonyl-L-valinol.

Benzyl chloroformate (91.0 g, 95% purity) was added dropwise over a period of 1 hr to a pre-cooled (0°) solution of L-valinol (50.0 g) and triethylamine (60.0 g) in chloroform (1500 ml). The reaction mixture was stirred for 1 hr at 0° and then allowed to warm to room temperature over 2 hr. After the reaction mixture was evaporated, ethyl acetate (1500 ml) was added to the residue; and the organic solution was washed with 1N NaOH and brine, dried (MgSO<sub>4</sub>), and evaporated. The resulting residue was purified by flash chromatography, using a stepwise gradient of ether:hexane (1:5) followed by ether, to give the product (91.4 g) as a white waxy solid; TLC, R<sub>f</sub>=0.23, hexane:ether (50:50).

#### b. N-Benzoyloxycarbonyl-L-valinal.

A solution of dimethylsulfoxide (107.2 g) in methylene chloride (150 ml) was added dropwise over 0.5 hr to a precooled (-60°), stirred solution of oxalyl chloride (87.1 g) in methylene chloride (800 ml) under a nitrogen atmosphere. The temperature of the mixture rose to -45°. The reaction mixture was then warmed to -30°. A solution of the product of Example 1a (81.5 g) in methylene chloride (300 ml) was added dropwise over 45 min at -30°. The reaction mixture was stirred for 50 min at -25°, cooled to -40° and a solution of diisopropylethylamine (177.4 g) in methylene chloride (250 ml) was added dropwise over 45 min at -40°. The reaction mixture was stirred for 1 hr as it warmed to room temperature. The reaction mixture was diluted with methylene chloride (1500 ml), and the organic phase was washed with 1N HCl and evaporated to give the product (98 g) as a green oil which was used immediately without further purification; TLC, R<sub>f</sub>=0.48, hexane:ether (50:50).

#### c. N-Benzoyloxycarbonyl-L-valinal diethylacetal.

Triethyl orthoformate (508 g), absolute ethanol (800 ml) and p-toluenesulfonic acid monohydrate (5.0 g) were added to a portion of the product of Example 1b (81 g). The mixture was stirred for 10 min at room temperature and then evaporated. The resulting residue was dissolved in ether, washed with saturated aqueous NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated to give a crude product which was purified by flash chromatography using a stepwise gradient of hexane through mixtures of methylene chloride:hexane to ethyl acetate:methylene chloride (30:70) to give the product (84.7%) as a pale yellow oil; TLC, R<sub>f</sub>=0.21,

methylene chloride:petroleum ether (50:50).

d. L-Valinal diethylacetal (Formula VIII).

- 5 A mixture of the product prepared using the method of Example 1c (147.8 g) and 10% palladium on carbon (10 g) in ethyl acetate (1500 ml) was stirred under  $H_2$  (1 bar) until 2500 ml of  $H_2$  were consumed. Twice during this time the reaction was interrupted and 10% palladium on carbon (10 g) was added. The reaction mixture was then filtered through a pad of diatomaceous earth. 10% Palladium on carbon (10 g) was added and the reaction mixture was again stirred under  $H_2$  until 10.92 liters of  $H_2$  were consumed. The reactions mixture was filtered through diatomaceous earth and the filtrate was concentrated under vacuum to give the product (78.8 g) as a pale yellow oil;  $\alpha_D^{25} = +7.8$ .

e. Benzylloxycarbonyl-L-valyl-L-proline methyl ester.

- 15 To a cooled (0-5°) solution of N-benzylloxycarbonyl-L-valine (450.0 g) in dry N,N-dimethylformamide (3.0 liter) was added 1-hydroxybenzotriazole hydrate (483.3 g); and the reaction mixture was stirred for 20 min, followed by the addition of a slurry of L-proline methyl ester hydrochloride (296.4 g) and triethylamine (186.6 g) in N,N-dimethylformamide (1.5 liter). After the resulting mixture was cooled to 0°, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (377.6 g, 1.97 mol) in N,N-dimethylformamide (500 ml) was added. The reaction mixture was stirred at 0-5° for 3 hr and then allowed to warm gradually to room temperature. Stirring was continued for 65 hr, and the mixture was filtered and evaporated. The residue was partitioned between ether and 1N HCl, and the precipitate which formed was removed by filtration. The ethereal layer was then separated; washed with water, saturated aqueous  $NaHCO_3$  and brine; dried ( $MgSO_4$ ); and evaporated. The crude ester was purified by flash chromatography using a gradient elution of methylene chloride, then methanol:methylene chloride (1:99), (2.5:79.5), and, finally, (5:95). The impure material from the first column was rechromatographed using a gradient elution of methylene chloride:hexanes (1:3), methylene chloride, and, finally, methanol: methylene chloride (2:98). The combined chromatographies afforded the ester (596.9 g, 92%) as a colorless oil; TLC,  $R_f = 0.45-0.60$ , methanol:methylene chloride (5:95); MS,  $m/e = 363(M+1, \text{base}), 319, 255, 130, 91$ .

Analysis for $C_{19}H_{26}N_2O_5 \cdot 0.25 H_2O$ :			
Calculated:	C, 62.19;	H, 7.28	N, 7.68
Found:	C, 62.19;	H, 7.12;	N, 7.51

f. Benzylloxycarbonyl-L-valyl-L-proline (Formula IX).

- 40 To a solution of the product of Example 1e (595.0 g) in methanol (4.8 liter) was added 1N NaOH (1.80 liter), and the solution was stirred for 18 hr. The methanol was evaporated, and the aqueous layer was acidified (pH 2) with 1N HCl and extracted with methylene chloride. The organic extracts were washed with brine, dried ( $Na_2SO_4$ ) and evaporated to afford the acid (520.2 g, 90%) as an analytically pure, white solid; MS,  $m/e = 349(M+1, \text{base}), 305, 241, 206, 116, 91$ .

Analysis for $C_{18}H_{24}N_2O_5 \cdot 0.3 H_2O$ :			
Calculated:	C, 61.11;	H, 7.01	N, 7.92
Found:	C, 61.12;	H, 6.86;	N, 7.68

g. (S)-Benzylloxycarbonyl-L-valyl-N[(diethoxymethyl)-2-methylpropyl]-L-prolinamide (Formula X).

- 55 Isobutyl chloroformate (57.8 g) was added in one portion to a solution of the product of Example 1f (154.3 g) and 4-methylmorpholine (42.8 g) in dry tetrahydrofuran (280 ml) at -20°. After stirring for 10 min, the mixture was cooled to -40° and aminoacetate prepared as described in Example 1, parts a-d (74.2 g) in tetrahydrofuran (700 ml) was added. The mixture was allowed to warm to room temperature and stir for 16 hr before it was filtered and evaporated. The residue was dissolved in ethyl acetate, washed with 1N HCl,

saturated aqueous  $\text{NaHCO}_3$  and brine; dried ( $\text{Na}_2\text{SO}_4$ ); and evaporated. The crude product was purified by flash chromatography eluting with a gradient of methylene chloride, then ethyl acetate: methylene chloride (4:96), (8:92), (25:75), (50:50), and, finally, ethyl acetate to afford 156 g of product. The impure fractions were rechromatographed on a high pressure liquid chromatograph (Waters Prep 500 HPLC using 2 silica gel cartridges), eluting with ethyl acetate:methylene chloride, to afford an additional 22 g of product; TLC,  $R_f=0.47$ , ethyl acetate:methylene chloride (25:75).

h. (S)-Benzyloxycarbonyl-L-valyl-N-(1-formyl-2-methylpropyl)-L-prolinamide (Formula XI).

- 10 A solution of the product of Example 1g (16.97 g) in acetone (800 ml) was added to a solution of concentrated HCl (45 ml) in water (2.6 liter), and the solution was stirred at room temperature for 16 hr. Ethyl acetate was added and the aqueous layer was extracted with ethyl acetate. The organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated to afford 12.8 g of yellowish oil; TLC,  $R_f=0.61$ , ethyl acetate:hexanes (4:1); MS,  $m/e=432(M+1, \text{base})$ , 199.

- 15 h-1. A preferred method for conversion of the acetal product of Example 1g into the aldehyde product of Example 1h is as follows:

- 20 To a stirred solution of the acetal product of Example 1g (18.60 g) in acetone (500 ml) under nitrogen was added p-toluenesulfonic acid (360 mg). The mixture was stirred 23 hr and the solvent evaporated. The residue was diluted with ethyl acetate and washed (saturated sodium bicarbonate, brine), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to afford 15.68 g (97%) of the aldehyde product of Example 1h; TLC,  $R_f=0.48$ , acetone:hexanes (45:55); MS,  $m/e=460(M+29)$ , 433 ( $M+2$ ), 432( $m+1$ ), 331 199.

- 25 i. Benzyloxycarbonyl-L-valyl-N-[1-(cyanohydroxymethyl)-2-methylpropyl]-L-prolinamide (Formula XIII,  $W=\text{CN}$ ).

- 30 Solid KCN (7.74 g, 119 mmol) was added to a solution of the product of Example 1h, (12.8 g) in tetrahydrofuran (150 ml) and water (128 ml). The resulting mixture was stirred for 4.5 hr, and then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with saturated aqueous  $\text{NaHCO}_3$  brine, dried (10% (w/w)  $\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$ ) and evaporated to afford 14.0 g of crude cyanohydrin; TLC,  $R_f=0.17$ , acetone:hexanes (1:3).

- 35 i-1. An alternative, preferred procedure for preparation of the product of Example 1i is described in Example 4a.

- j. Benzyloxycarbonyl-L-valyl-N-[1-(2-benzoxazolyl)-hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=2-benzoxazolyl).

- 40 A solution of acetyl chloride (9.50 ml) in ether (15 ml) was added to a solution of absolute ethanol (10.8 ml) in ether (33 ml) at  $0^\circ$  over a period of 20 min. After stirring for 4.5 hr, and the solvent evaporated, the residue was dissolved in absolute ethanol (80 ml), and 2-aminophenol (1.83 g) was added. After heating at  $60^\circ$  for 3 hr, the mixture was dissolved in ethyl acetate, washed with 1N NaOH and brine, dried (10% (w/w)  $\text{K}_2\text{CO}_3/\text{Na}_2\text{SO}_4$ ), and evaporated. The crude product was flash chromatographed, eluting with acetone:hexanes (3:17), to afford 3 fractions of yellowish foam: fraction one, TLC,  $R_f=0.30$ , acetone:hexane (3:17), all four isomers, 1.77 g; fraction 3, TLC,  $R_f=0.17$ -  
45 fraction two, TLC,  $R_f=0.25$ -0.17, acetone:hexane (3:17), one isomer, 136 mg;  
50 0.08, acetone:hexane (3:17), three isomers, 2.45 g.

k. L-Valyl-N-[1-(2-benzoxazolyl)-hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XV, heterocycle containing X, N and Q=2-benzoxazolyl).

- 55 A mixture of 10% palladium on carbon (300 mg, 50% water wet) and the product of Example 1j, fraction three (2.45 g) in ethanol (100 ml) was hydrogenated in a shaker at 3.4 bar for 6 hr after which time an additional amount of palladium on carbon (300 mg) was added and the mixture hydrogenated for an additional 3 hr. The mixture was filtered through diatomaceous earth and the solvent evaporated. The

residue was dissolved in ethyl acetate, extracted into 1N HCl and the aqueous acid layer was washed with ethyl acetate, basified with 1N NaOH and, extracted with ethyl acetate. The organic solvent was evaporated to afford 1.40 g (76%) of solid.  $R_f$  = 0.0-0.15, methanol:chloroform (1:19); MS  $m/e$  = 471 ( $M+1$ ), 399.

- 5 I. [4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = *p*-phenylene,  $R^4 = R^5$ ,  $S(O_2).NH.CO-$ ,  $R^5 = 4-ClC_6H_4$ ).

- 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (710 mg) was added to a solution of the product of  
 10 Example 1k (1.38g), 1-hydroxybenzotriazole (983 mg) and 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoic acid (see parts n and o below) (1.12 g) in tetrahydrofuran (18 ml), and the solution was stirred at room temperature for 16 hr. The mixture was partitioned between water and ethyl acetate; the organic phase was washed with 1N HCl and brine, dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography, eluting with ethyl acetate:ether:acetic acid (60:40:2 drop/ml), to afford 1.2 g of solid; TLC,  
 15  $R_f$  = 0.42, methanol:chloroform:acetic acid (5:95:1 drop/ml); MS,  $m/e$  = 738( $M+1$ ), 421, 318.

Analysis for $C_{32}H_{43}ClN_6O_8$ S.1.4 H <sub>2</sub> O:			
Calculated:	C, 56.64;	H, 5.85;	N, 9.17
Found:	C, 56.97;	H, 5.39;	N, 8.67

- 25 m. (S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = *p*-phenylene,  $R^4 = R^5$ ,  $S(O_2).NH.CO-$ ,  $R^5 = 4-ClC_6H_4$ ).

- Trifluoroacetic acid (0.712 ml) was added to a solution of the product of Example 1, part 1 (1.15 g) and Dess-Martin periodinane (2.65 g) in methylene chloride (15 ml); and the solution was stirred at room temperature for 16 hr. The resulting suspension was partitioned between ethyl acetate and 1N HCl. The  
 30 organic solution was washed with two portions of 1:1 (w/w) saturated aqueous  $Na_2S_2O_3$ :  $NaHCO_3$ , saturated aqueous  $NaHCO_3$  and brine, dried ( $MgSO_4$ ) and evaporated. The crude product was purified by flash chromatography eluting with tetrahydrofuran:methylene chloride:acetic acid (2.5:97.5:1 drop/ml) to afford 889 mg of solid. A second purification was performed using flash chromatography on acidic silica gel, eluting with methanol:chloroform (2.5:97.5), to afford the title compound (701 mg) as a solid; TLC,  $R_f$  = 0.47,  
 35 ethyl acetate:hexanes:acetic acid (65:35:1 drop/ml); HPLC,  $t_R$  = 9.27, Col. B, FR = 4, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS,  $m/e$  = 736( $M+1$ ), 718, 421, 298.

Analysis for $C_{35}H_{48}ClN_6O_8$ S.1.25 H <sub>2</sub> O:			
Calculated:	C, 56.12;	H, 5.47;	N, 9.09
Found:	C, 56.24;	H, 5.07;	N, 8.74

The benzoic acid intermediate used for coupling in part 1, may be prepared as follows:

- 45 n. 1,1-Dimethylethyl 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoate.

- A 5-liter 3-neck round bottom flask was equipped with a mechanical stirrer and nitrogen inlet. Methylene chloride (2 liters) was placed in the reaction flask and terephthalic acid mono-*t*-butyl ester (127.5 g), 4-dimethylaminopyridine (70.06 g), and 4-chlorobenzenesulfonamide (110.04 g) were added sequentially using methylene chloride (400 ml) to wash down the solids. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide  
 50 hydrochloride was added in portions over 10 min using methylene chloride (100 ml) to wash down the solid. After the reaction mixture was stirred overnight at room temperature, it was evaporated to dryness. The residue was partitioned between ethyl acetate and water. The organic solution was washed with 20% (w/v) aqueous citric acid, saturated aqueous  $NaHCO_3$  and brine; dried ( $Na_2SO_4$ ); and evaporated to a white solid.  
 55 After drying in a vacuum oven at 50°, the ester (277g, 100%) was obtained in a sufficiently pure state to be used directly for the next step; TLC,  $R_f$  = 0.43, methanol:chloroform (15:85). Further purification was possible by recrystallization from ethanol/water; mp above 300°).

o. 4-[(4-Chlorophenyl)sulfonylamino]benzoic acid.

A 3-liter 3-neck round bottom flask was equipped with a mechanical stirrer and a  $\text{CaCl}_2$  drying tube. Trifluoroacetic acid (1300 g) was added and cooled to  $0^\circ$ , and the product of Example 1n (79.5 g) was added. Initially, the solid dissolved, giving a clear solution. After 10-15 min, a heavy precipitate of product formed; and it was difficult to stir the reaction mixture. Vigorous stirring with the mechanical stirrer was essential to drive the reaction to completion. The reaction mixture was stirred at  $0-5^\circ$  for 1 hr before it was poured into 1500 ml of ice/water and stirred for 2 hr. The resulting solid was filtered and dried. The white solid (61.5 g, 91%) obtained was recrystallized from 1600 ml absolute ethanol/1600 ml water to yield the benzoic acid (54 g, 80%) as white needles; mp  $286-288^\circ$ ; TLC  $R_f = 0.7$ , methanol:chloroform:acetic acid (10:90:1).

#### Example 2

[4-(Methylsulfonylamino)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene,  $R^4=R^5, S(O_2)-NH.CO-$ ,  $R^5=CH_3$ ).

a. (1S)-[4-(1,1-Dimethylethoxy)carbonylbenzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XVII, heterocycle containing X, N and Q=2-benzoxazolyl,  $R^7.LA=4\{[(CH_2)_3COCO]C_6H_4CO\}$ ).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (510 mg) was added to a solution of product prepared by the method of Example 1k [material prepared according to the method of Example 1j and obtained in the (1S)-form] was treated according to the procedure of Example 1k and obtained in the (1S)-form] (1.00 g), 1-hydroxybenzotriazole (720 mg), and terephthalic acid mono-t-butyl ester (560 mg) in tetrahydrofuran (5 ml) at  $0^\circ$ ; and the solution was allowed to warm to room temperature and stirred for 16 hr. The mixture was partitioned between water and ethyl acetate, the organic phase was washed with 1N HCl (twice), saturated sodium bicarbonate (twice) and brine, dried ( $\text{MgSO}_4$ ) and evaporated. The crude product was purified by flash chromatography, eluting with acetone:hexane (4:6), to afford the product (1.08 g, 73%) as a solid; TLC,  $R_f = 0.7$ , acetone:hexane (45:55); MS,  $m/e = 621 (M+1)$ , 649, 622, 565, 318.

Analysis for $C_{34}H_{44}N_4O_7 \cdot 0.4 H_2O$ :			
Calculated:	C, 65.03;	H, 7.19;	N, 8.92
Found:	C, 65.06;	H, 7.05;	N, 8.72

b. (S)-[4-(1,1-Dimethylethoxy)carbonylbenzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula IV, heterocycle containing X, N and Q=2-benzoxazolyl,  $R^7.LA=4\{[(CH_2)_3COCO]C_6H_4CO\}$ ).

t-Butyl alcohol (0.030 ml) was added to a solution of the product of Example 3a (200 mg) and Dess-Martin periodinane (410 mg) in methylene chloride (5 ml) and the solution stirred at room temperature for 16 hr. The resulting solution was partitioned between ethyl acetate and 1:1 saturated  $\text{Na}_2\text{S}_2\text{O}_3:\text{NaHCO}_3$ . The organic phase was separated and washed with 1:1 saturated  $\text{Na}_2\text{S}_2\text{O}_3:\text{NaHCO}_3$  (twice) and brine, dried [ $\text{K}_2\text{CO}_3:\text{Na}_2\text{SO}_4$  (1:2, w:w)] and evaporated. The crude product was purified by flash chromatography, eluting with acetone:hexanes (1:3) to afford the product (161 mg, 80%) as a solid; TLC,  $R_f = 0.35$ , acetone:hexanes (1:3); HPLC,  $t_R = 7.86$ , Col A, FR=2, water:acetonitrile (40:60); MS,  $m/e = 619 (M+1)$ , 563,



316, 304, 204, 120, 115.

5	Analysis for $C_{24}H_{42}N_4O_7 \cdot 0.4 H_2O$ :			
	Calculated:	C, 65.24;	H, 6.89;	N, 8.95
	Found:	C, 65.26;	H, 6.74;	N, 8.84

c. (4-Carboxybenzoyl)-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula IV, heterocycle containing X, N and Q = 2-benzoxazolyl, R<sup>7</sup>. L.A. = 4-(HOOC)C<sub>6</sub>H<sub>4</sub>CO).

A solution of the product of Example 3b (770 mg) in trifluoroacetic acid (5 ml) was stirred at room temperature for 2 hr. The solvent was then evaporated. The residual oil was diluted with ether and the resulting solution was evaporated. This process was repeated 6 times. The brown oil was then placed under high vacuum for 48 hr. The crude acid (now a foam) was purified by flash chromatography, eluting with acetone:hexane:acetic acid (40:60:1) to afford the product (680 mg, 96%) as a yellow solid; TLC, R<sub>f</sub> = 0.23, acetone:hexane:acetic acid (4:6:1 drop/ml); MS, m/e = 563 (M+1), 545, 316, 298, 248, 245, 220, 204, 149, 148, 120.

20	Analysis for $C_{30}H_{34}N_4O_7 \cdot 0.2 NaOH \cdot 0.55 H_2O$ :			
	Calculated:	C, 62.07;	H, 6.13;	N, 9.65
	Found:	C, 61.70;	H, 5.95;	N, 9.82

d. [4-(Methylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = p-phenylene, R<sup>4</sup> = R<sup>5</sup>. S(O<sub>2</sub>).NH.CO-, R<sup>6</sup> = CH<sub>3</sub>).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (78 mg) was added to a solution of the product of Example 3c (200 mg), 4-dimethylaminopyridine (58 mg), and methanesulfonamide (37 mg) in methylene chloride (2 ml), and the solution stirred at room temperature for 16 hr. After the solvents were evaporated, the residue was partitioned between ethyl acetate and 1N HCl. The organic layer was separated, washed with 1N HCl, dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography, eluting with ethyl acetate:ether:acetic acid (20:80:1) to afford the product (74.2 mg, 32%) as a solid, TLC, R<sub>f</sub> = 0.10, ether:acetic acid (100:1); HPLC, t<sub>R</sub> = 6.03, Col B, FR = 2, water:acetonitrile:tetrahydrofuran: trifluoroacetic acid (55:35:13:0.1); MS, m/e = 640 (M+1), 622, 326, 325, 316, 298, 247, 201.

40	Analysis for $C_{31}H_{37}N_5O_8 \cdot 0.8 CH_3CO_2H$ :			
	Calculated:	C, 56.93;	H, 5.89;	N, 10.18
	Found:	C, 57.22;	H, 5.97;	N, 9.79

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## Example 3

(S)-[4-(Phenylsulfonylaminocarbonyl)benzoyl]-L-valyl-  
N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-pro-  
linamide (Formula I, heterocycle containing X, N and  
Q=2-benzoxazolyl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).-  
NH.CO-, R<sup>5</sup>=C<sub>6</sub>H<sub>5</sub>).

a. 4-(Phenylsulfonylaminocarbonyl)benzoic acid.

Using similar procedures to those described in Example 1 parts n and o, except using benzenesul-  
fonamide in place of 4-chlorobenzenesulfonamide, the benzoic acid was obtained as a solid; mp 259-261°.

b. (1S)-[4-(Phenylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methyl-  
propyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-  
phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, R<sup>5</sup>=C<sub>6</sub>H<sub>5</sub>).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg) was added to a solution of the  
product of Example 1k (200 mg), 1-hydroxybenzotriazole (200 mg), and 4-(phenylsulfonylaminocarbonyl)-  
benzoic acid (179 mg) in tetrahydrofuran (4 ml), and the solution stirred at room temperature for 16 hr. The  
mixture was partitioned between water and ethyl acetate. The organic phase was washed with saturated  
NaHCO<sub>3</sub> (3 times) and brine, dried (MgSO<sub>4</sub>) and evaporated. The aqueous layers were combined, acidified  
to pH 1 with concentrated HCl, and extracted with chloroform. The chloroform phase was dried  
[K<sub>2</sub>CO<sub>3</sub>:Na<sub>2</sub>SO<sub>4</sub> (1:2, w:w)] and evaporated. The crude product obtained from both the ethyl acetate and  
chloroform solutions was combined and purified by flash chromatography, eluting with ac-  
etone:hexanes:acetic acid (45:55:1), to afford the product (270 mg, 60%) as a solid; R<sub>f</sub>=0.15, ac-  
etone:hexanes:acetic acid (30:70:1 drop/ml); MS, m/e = 704 (M+1), 686, 387, 346, 318, 316, 300, 158, 120.

Analysis for C <sub>35</sub> H <sub>41</sub> N <sub>5</sub> O <sub>7</sub> S 0.8 CH <sub>2</sub> CO <sub>2</sub> H:			
Calculated:	C, 58.79;	H, 6.03;	N, 9.07
Found:	C, 59.11;	H, 6.02;	N, 8.88

c. (S)-[4-(Phenylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-  
prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene,  
R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, R<sup>5</sup>=C<sub>6</sub>H<sub>5</sub>).

Trifluoroacetic acid (0.09 ml) was added to a solution of the product of Example 4b (270 mg) and Dess-  
Marten periodinane (490 mg) in methylene chloride (5 ml) and the solution stirred at room temperature for  
16 hr. The resulting solution was diluted with ethyl acetate and washed (4 times with 4:1 brine: saturated  
Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>: Na<sub>2</sub>HCO<sub>3</sub> (1:1), once with brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified  
by flash chromatography, eluting with acetone:hexanes:acetic acid (40:60:1). The solid obtained from this  
column was further purified by flash chromatography on acidic silica gel eluting with chloroform to afford  
the title compound (152 mg, 57%) as a solid; TLC, R<sub>f</sub>=0.23, acetone:hexanes:acetic acid (40:60:1); HPLC,  
t<sub>R</sub>=10.09, Col B, FR=2, water: acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS, m/e = 702  
(M+1), 326, 299, 286, 297, 201, 136.

Analysis for $C_{35}H_{39}N_3O_8S_0.75NaOH.0.25H_2O$ :			
Calculated:	C, 58.72;	H, 5.51;	N, 9.51
Found:	C, 58.38;	H, 5.34;	N, 9.28

5

Example 4

10 (S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzo-  
yl]-L-valyl-N-[1-(5-methoxybenzoxazol-2-yl)carbonyl-  
2-methylpropyl]-L-prolinamide (Formula I, heterocycle  
15 containing X, N and Q=5-methoxybenzoxazol-2-yl, A=CO,  
L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

20 a. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(cyanhydroxymethyl)-2-methylpropyl]-L-prolinamide (Formula XIII, W=CN).

An alternative, preferred procedure for preparation of the product of Example 1i is as follows: A 250 ml  
25 round bottom flask with stirrer was dried under vacuum and purged with nitrogen. The flask was charged  
with dichloromethane (120 ml) followed by the addition of aldehyde prepared as described in Example 1h -  
(17.7g) and triethyl amine (3.4 ml). Acetone cyanohydrin (11.0 ml) was added in one portion. The reaction  
mixture was stirred for 21 hr. The crude reaction mixture was diluted with dichloromethane. This solution  
30 was carefully washed (twice with saturated ammonium chloride, once with brine), dried ( $MgSO_4$ ), and the  
solvent evaporated. The crude product was dissolved in ethyl acetate, washed (once with saturated  
ammonium chloride, once with brine), dried ( $MgSO_4$ ), and evaporated. The resulting foam was heated to  
50° under vacuum for four days to afford 18.90 g (100%) of product: TLC,  $R_f$ =0.31, acetone:hexanes  
(40:60).

35 b. (1S)-Benzyloxycarbonyl-L-valyl-N-[3-ethoxy-2-hydroxy-3-imino-1-(1-methylethyl)propyl]-L-prolinamide hydrochloride (Formula XIII, W=C(NH)OR, R=C<sub>2</sub>H<sub>5</sub>).

To a stirred solution of ethanol (79.4 ml) in chloroform (80 ml) at 0° under nitrogen was added  
dropwise acetyl chloride (87.7 ml) over the course of 25 min. The product of Example 4a (18.81 g) in  
40 chloroform (80 ml) was added and the reaction stirred at 0° for 4 hr. The solvents were evaporated to  
afford the product (20.89 g); TLC, after partitioning an aliquot between ethyl acetate and 1N NaOH to form  
the free imino ether,  $R_f$ =0.45, methanol:chloroform (7.5:92.5).

c. 2-Amino-4-methoxyphenol.

45 A mixture of 10% (w/w) palladium on carbon (200 mg) and 4-methoxy-2-nitrophenol (3.0 g) in ethanol  
(100 ml) was hydrogenated in a shaker at 3.4 bar for 24 hr. The mixture was filtered through diatomaceous  
earth and evaporated to give the product (2.3 g); TLC,  $R_f$ =0.61, methanol:chloroform (1:9); MS, m/e = 170-  
(M+1), 164, 152(base), 124.

50 d. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(hydroxy)-(5-methoxybenzoxazol-2-yl)methyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=5-methoxybenzoxazol-2-yl).

A stirred solution of the imide of Example 4b (6.35 g) and 2-amino-4-methoxyphenol (1.525 g) in dry  
ethanol (40 ml) was heated for 8 hr at 60° under nitrogen. The mixture was dissolved in ethyl acetate,  
55 washed (1N HCl, saturated sodium bicarbonate, brine), dried (10% (w/w)  $K_2CO_3/N_2SO_4$ ), and evaporated.  
The crude product was flash chromatographed eluting with acetone:hexanes (30:70) to afford the product  
(983 mg). The mixed fractions were combined, evaporated and flash chromatographed eluting with  
acetone:hexanes (35:65) to afford additional product (588 mg); TLC,  $R_f$ =0.28, acetone:hexanes (40:60); MS,

m/e = 582(M + 2), 581(M + 1), 563, 473, 331, 261, 195, 107, 91, 79, 70.

e. (1S)-L-Valyl-N-[1-(hydroxy) (5-methoxybenzoxazol-2-yl)methyl-2-methylpropyl]-L-prolinamide (Formula XV, heterocycle containing X, N and Q = 5-methoxybenzoxazol-2-yl).

A mixture of 10% (w/w) palladium on carbon (300 mg) and the product from Example 4d (1.54 g) in ethanol (100 ml) was hydrogenated in a shaker at 3.4 bar for 4 hr, after which time the mixture was filtered through diatomaceous earth and the solvent evaporated. The residue was redissolved in ethanol (100 ml), 10% palladium on carbon (0.69 g) added and the mixture hydrogenated in a shaker at 3.4 bar for 4 hr. The mixture was then filtered through diatomaceous earth and the solvent evaporated to afford 990 mg (83%) of solid ( $R_f$  = 0.0, methanol:chloroform (1:19); MS, m/e = 475(M + 29), 447(M + 1), 429, 348, 234, 233, 197, 180, 179, 178, 155, 150, 100, 72, 70.

f. (1S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[1-(hydroxy)(5-methoxybenzoxazol-2-yl)methyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q = 5-methoxybenzoxazol-2-yl, A = CO, L = p-phenylene,  $R^4 = R^5$ . S(O)<sub>2</sub>.NH.CO-,  $R^6 = 4\text{-ClC}_6\text{H}_4$ ).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (470 mg) was added to a solution of the product of Example 4e (990 mg), 1-hydroxybenzotriazole (330 mg), and the product of Example 1 part o - (830 mg) in tetrahydrofuran (7 ml); and the solution was stirred at room temperature for 16 hr. The reaction mixture was then stored at -78° for 36 hr. The reaction mixture was diluted with ethyl acetate, washed (saturated sodium bicarbonate, 1N HCl, brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The resulting solid was redissolved in ethyl acetate, washed (saturated sodium bicarbonate, 1N HCl, brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The crude product was purified by flash chromatography eluting with acetone:chloroform:acetic acid (20:80:1) to afford the product (976 mg) as a solid; TLC,  $R_f$  = 0.25, acetone:chloroform:acetic acid (35:65:1); MS, m/e = 768(M + 1), 752, 751, 750, 423, 422, 421, 402, 377, 348, 330.

Analysis for C <sub>37</sub> H <sub>42</sub> ClN <sub>5</sub> O <sub>9</sub> S.1.8 CH <sub>3</sub> CO <sub>2</sub> H:			
Calculated:	C, 55.97;	H, 5.63;	N, 8.16
Found:	C, 56.14;	H, 5.76;	N, 7.95

g. (S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[1-(5-methoxybenzoxazol-2-yl)-carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 5-methoxybenzoxazol-2-yl, A = CO, L = p-phenylene,  $R^4 = R^5$ . S(O)<sub>2</sub>.NH.CO-,  $R^6 = 4\text{-ClC}_6\text{H}_4$ ).

t-Butanol (0.116 ml) was added to a solution of the product of Example 4f (947.6 mg) and Dess-Martin periodinane (1.57 g) in dichloromethane (6 ml), and the solution stirred at room temperature for 21 hr. The resulting suspension was diluted with ethyl acetate and washed (twice with 1:1 saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>: saturated NaHCO<sub>3</sub>, once with 1N HCl, brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography eluting with acetone:hexane:acetic acid (50:50:1) to afford the product (703 mg) as a solid; TLC,  $R_f$  = 0.47, ethyl acetate:hexanes:acetic acid (65:35:1); MS, m/e = 766(M + 1), 750, 749, 748, 422, 421, 329, 328, 327, 326, 249, 231.

Analysis for C <sub>37</sub> H <sub>38</sub> ClN <sub>5</sub> O <sub>9</sub> S.1.1 H <sub>2</sub> O.1.1 CH <sub>3</sub> CO <sub>2</sub> H:			
Calculated:	C, 55.26;	H, 5.51;	N, 8.22
Found:	C, 55.16;	H, 5.20;	N, 8.08

## Example 5

(S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzo-  
yl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl-  
2-methylpropyl]-L-prolinamide (Formula I, heterocycle  
containing X, N and Q=5-hydroxybenzoxazol-2-yl, A=CO,  
L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

Boron tribromide (3.55 ml, 1.0M in dichloromethane) was added to a solution of the product of Example 4g (680 mg) in dichloromethane (5 ml) at 0° and allowed to warm to room temperature. After 3 hours, the reaction mixture was partitioned between ethyl acetate and 1N HCl. The ethyl acetate layer was washed (brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with methanol:chloroform:acetic acid (1:98:1) to give the product (236 mg, 35%) as a yellow solid; TLC,  $R_f=0.28$ , methanol:chloroform:acetic acid (5:94:1); HPLC,  $t_R=6.75$ , Col. A,  $FR=3$ , water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS,  $m/e=752(M+1)$ , 734, 421, 377, 342, 314(base).

Analysis for  $C_{36}H_{38}ClN_5O_7S.O.2 CHCl_3.O.3 CH_3COOH.1.5 H_2O$ :

Calculated:	C, 53.83;	H, 5.20;	N, 8.53
Found:	C, 53.65;	H, 4.96;	N, 8.37

## Example 6

[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-  
valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]carbonyl-  
2-methylpropyl]-L-prolinamide (Formula I, heterocycle  
containing X, N and Q=5-(aminocarbonyl)benzoxazol-2-  
yl, A=CO, L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  
 $R^5=4-ClC_6H_4$ ).

## a. 3-Amino-4-hydroxybenzamide.

A solution of 3-amino-4-hydroxybenzoic acid (7.73 g) in thionyl chloride (96 ml) was stirred vigorously under nitrogen at 40° for one hour. The thionyl chloride was removed by distillation under reduced pressure and the resulting solid was suspended in toluene (350 ml). Anhydrous  $NH_3$  was bubbled into the reaction mixture for 45 minutes. The mixture was filtered through diatomaceous earth and the filter cake was washed copiously with acetone until fresh filtrate was clear. The acetone solution was evaporated, and the crude product was flash chromatographed eluting with acetone:chloroform (1:1) to afford the product (1.2 g) as a solid; TLC,  $R_f=0.17$  acetone:chloroform (60:40); MS,  $m/e=193(M+41)$ , 181( $M+29$ ), 153( $M+1$ ), 138, 110.

b. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(5-aminocarbonyl)benzoxazol-2-yl]hydroxymethyl-2-methylpropyl]-K-prolinamide (Formula XIV, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl).

A stirred solution of the imide of Example 4b (3.81 g) and 3-amino-4-hydroxybenzamide (1.00 g) in dry ethanol (28 ml) was heated for 2 hr at 60 ° under nitrogen. The mixture was dissolved in ethyl acetate, washed (twice with water, once with saturated sodium bicarbonate, brine), dried (MgSO<sub>4</sub>), and evaporated. The crude product was flash chromatographed eluting with acetone:chloroform (60:40) to afford the product (836 mg); TLC, R<sub>f</sub> = 0.42, tetrahydrofuran:chloroform (75:25); MS, m/e = 622(M+29), 595(M+2), 594(M+1), 505, 478, 477.

Analysis for C <sub>31</sub> H <sub>33</sub> N <sub>5</sub> O <sub>7</sub> ·2.0 H <sub>2</sub> O:			
Calculated:	C, 59.13;	H, 6.88;	N, 11.12
Found:	C, 59.18;	H, 6.35;	N, 11.04

c. (1S)-L-Valyl-N-[1-(5-(aminocarbonyl)benzoxazol-2-yl)]hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XV, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl).

A mixture of 10% (w/w) palladium on carbon (750 mg) and the product from Example 6b (0.920 g) in ethanol (150 ml) was hydrogenated in a shaker at 3.4 bar for 4 hr after which time the mixture was filtered through diatomaceous earth and the solvent evaporated. The residue was then redissolved in methanol and evaporated to afford the product (680 mg, 100%) as a solid; TLC R<sub>f</sub> = 0.0, methanol:chloroform (5:95); MS, m/e = 460(M+1), 247, 225, 198, 197, 196, 154, 125, 91.

d. (1S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[1-(5-(aminocarbonyl)benzoxazol-2-yl)]hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene, R<sup>4</sup> = R<sup>5</sup> = S(O<sub>2</sub>).NH.CO-, R<sup>6</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (292 mg) was added to a solution of the product of Example 6c (670 mg), 1-hydroxybenzotriazole (206 mg), and the product of Example 1 - part c - (507 mg) in tetrahydrofuran (5 ml); and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate and washed three times with distilled water, once with 1N HCl, once with saturated sodium bicarbonate, and once with brine. The bicarbonate wash was acidified to pH 1 and (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The crude product was flash chromatographed eluting with tetrahydrofuran:chloroform:acetic acid (70:30:1). The resulting material was filtered through silica gel eluting with tetrahydrofuran:chloroform:acetic acid (30:70:0 to 30:70:1 to 100:0:1) to afford the product (350 mg) as a solid; TLC, R<sub>f</sub> = 0.55, tetrahydrofuran:chloroform:acetic acid (80:20:1); MS, m/e = 247, 197, 163.

e. [4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-(aminocarbonyl)benzoxazol-2-yl)]carboxyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene, R<sup>4</sup> = R<sup>5</sup> = S(O<sub>2</sub>).NH.CO-, R<sup>6</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>).

Pyridine (0.422 ml) was added to a suspension of chromium trioxide (261 mg) in dry dichloromethane (27 ml), and the mixture stirred at room temperature 30 min. Diatomaceous earth (0.5 g) was added to the mixture which was stirred 5 more min. The product from Example 6d (340 mg) in dry dimethylformamide (1.5 ml) was added, and the mixture was allowed to stir for 3.5 hr. The resulting suspension was filtered through diatomaceous earth and evaporated. The residue was lixiviated with chloroform and filtered through diatomaceous earth. (The use of methanol for lixiviation is preferred.) This process was repeated six times. The filtrates were combined and evaporated. The resulting solid was flash chromatographed eluting with tetrahydrofuran:chloroform:acetic acid (55:45:1). The resulting solid was filtered through silica gel, eluting first with chloroform then with tetrahydrofuran:acetic acid (99:1). The resulting solid was again flash chromatographed eluting with tetrahydrofuran:hexanes:acetic acid (60:40:1) to afford the product (37.5 mg); TLC, R<sub>f</sub> = 0.50, methanol:chloroform:acetic acid (10:90:1); HPLC, t<sub>R</sub> = 7.23, Col. A, FR = 1, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS, m/e = 777(M+1), 761, 421, 342, 341, 340, 339, 192.

Analysis for $C_{37}H_{33}ClN_6O_9S \cdot 0.90 H_2O \cdot 1.0 CH_3CO_2H$ :			
Calculated:	C, 54.75;	H, 5.28;	N, 9.82
Found:	C, 55.07;	H, 5.41;	N, 9.57

## Example 7

[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-  
L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]car-  
bonyl-2-methylpropyl]-L-prolinamide (Formula I,  
heterocycle containing X, N and Q=5-(hydroxymethyl)-  
benzoxazol-2-yl, A=CO, L=p-phenylene,  $R^4=R^5 \cdot S(O_2) \cdot$ -  
NH.CO-,  $R^5=4-ClC_6H_4$ ).

## a. 3-Amino-4-hydroxybenzyl alcohol.

A mixture of 10% (w/w) palladium on carbon (5.25 g) and 4-hydroxy-3-nitro-benzyl alcohol (25.0 g) in ethanol (1.3 liter) was hydrogenated in a shaker at 3.4 bar from 23 hr, after which time the mixture was filtered through diatomaceous earth and evaporated. The residue was flash chromatographed, eluting with methanol:chloroform (0:100 to 10:90), to afford the product (11.92 g, 60%) as a red solid; TLC,  $R_f=0.14$ , methanol:chloroform (5:95); MS,  $m/e=140(M+1)$ , 139, 138, 123, 122, 110.

b. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(hydroxy)[5-(hydroxymethyl)benzoxazol-2-yl]methyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N, and Q=5-(hydroxymethyl)benzoxazol-2-yl).

The product from Example 4b (3.0 g) and alcohols prepared according to Example 7a (0.771 g) in absolute ethanol (20 ml) were heated at 65° for 20 hr; the mixture was dissolved in ethyl acetate, washed (1N NaOH, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was flash chromatographed eluting with acetone:hexanes (55:45) to give the product (858 mg) as a white solid; TLC,  $R_f=0.26$ , acetone:hexanes (3:2); MS  $m/e=581(M+1)$ , 563, 501, 473, 455.

Analysis for $C_{51}H_{49}N_6O_7 \cdot 1.25 H_2O$ :			
Calculated:	C, 61.73;	H, 7.10;	N, 9.29
Found:	C, 61.81;	H, 6.86;	N, 9.09

c. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-[5-[(t-butyl)dimethylsilyloxy]methyl]benzoxazol-2-yl]-hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=5-[(t-butyl)dimethylsilyloxy]methyl]benzoxazol-2-yl).

A solution of the product of Example 7b (736 mg), t-butyl)dimethylsilyl chloride (380 mg), 4-dimethylaminopyridine (7.8 mg), and triethylamine (0.37 ml) in dichloromethane (10 ml) was stirred at room temperature for 16 hr. The solution was then dissolved in ethyl acetate, washed (1N HCl, saturated sodium bicarbonate, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography, eluting with acetone:hexanes (1:3), to afford the product (715 mg, 82%) as a light yellow solid; TLC,  $R_f=0.46$ , acetone:hexanes (2:3); MS,  $m/e=695(M+1)$ , 679, 587, 563, 455.

Analysis for $C_{37}H_{54}N_4O_7 \cdot 0.25 H_2O$ :			
Calculated:	C, 63.54;	H, 7.85;	N, 8.01
Found:	C, 63.44;	H, 7.75;	N, 7.54

d. (S)-Benzyloxycarbonyl-L-valyl-N-[1-[5-[(t-butylidimethylsilyloxy)methyl]benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q = 5-[(t-butylidimethylsilyloxy)methyl]benzoxazol-2-yl).

Tert-butyl alcohol (0.068 ml) was added to a solution of the product of Example 7c (500 mg) and Dess-Martin periodinane (1.22 g) in dichloromethane (5 ml) and the solution stirred at room temperature for 16 hr. The resulting suspension was partitioned between ethyl acetate and a 1:1 solution of saturated  $Na_2S_2O_3$ :saturated  $NaHCO_3$ ; the layers were separated; and the ethyl acetate layer washed (once with a 1:1 solution of saturated  $Na_2S_2O_3$ :saturated  $NaHCO_3$ , twice with saturated  $NaHCO_3$ , once with brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with acetone:hexanes (1:3) to afford the product (448 mg, 90%) as a white solid; TLC,  $R_f$  = 0.54, acetone:hexanes (2:3); HPLC,  $t_R$  = 6.18, Col A, FR = 2, water:acetonitrile (1:9); MS, m/e = 603(M+1, base), 677, 635, 585, 460.

Analysis for $C_{37}H_{52}N_4O_7 \cdot Si_0.25 H_2O$ :			
Calculated:	C, 63.72;	H, 7.59;	N, 8.03
Found:	C, 63.64;	H, 7.45;	N, 7.70

e. Benzyloxycarbonyl-L-valyl-N-[1-5-(hydroxymethyl)-benzoxazol-2-yl]carbonyl-2-methylpropyl-L-prolinamide (Formula VI, heterocycle containing X, N and Q = 5-(hydroxymethyl)benzoxazol-2-yl).

Tetrabutylammonium fluoride (1.2 ml of 1M solution in tetrahydrofuran) was added to a solution of the product of Example 7d (418 mg) in tetrahydrofuran (5 ml). The resulting red solution was stirred at room temperature for 10 min and stored at 5° for 16 hr. The red solution was partitioned between ethyl acetate and 1N HCl, and the ethyl acetate layer was washed (saturated sodium bicarbonate, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with acetone:hexanes (35:65) followed by a second purification by flash chromatography eluting with methanol:chloroform (2.5:97.5) to afford the product 183 mg, 53%) as a white solid; TLC,  $R_f$  = 0.52, acetone:hexanes (3:2); HPLC,  $t_R$  = 6.27, Col A, FR = 1, water:acetonitrile (40:60); MS, m/e = 579(M+1), 561, 331, 225, 197, 91 (base).

Analysis for $C_{31}H_{38}N_4O_7 \cdot 1.0 H_2O$ :			
Calculated:	C, 62.40;	H, 6.76;	N, 9.39
Found:	C, 62.23;	H, 6.40;	N, 9.14

f. [4-[(4-Chlorophenyl)sulfonylamino]benzoyl]benzoyl-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 5-(hydroxymethyl)benzoxazol-2-yl, A = CO, L = p-phenylene,  $R^1$  =  $R^2$  =  $S(O_2)$ -,  $NHCO$ -,  $RP$  = 4-ClC<sub>6</sub>H<sub>4</sub>).

Trifluoromethanesulfonic acid (0.140 ml) was added to a solution of material prepared according to the procedure of Example 7e (182 mg) in dichloromethane (8 ml), stirred for 15 min, and evaporated. The residue was dissolved in tetrahydrofuran (10 ml) and treated with 4-dimethylaminopyridine (293 mg), the product of Example 1 part a (113 mg), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (66.5 mg), and stirred at room temperature for 16 hr. The mixture was partitioned between 1N HCl and ethyl acetate; the ethyl acetate phase was washed (1N HCl, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with methanol:chloroform:acetic acid (1.5:97.5:1.0) to afford the product (77 mg, 32%) as a light yellow solid; TLC,  $R_f$  = 0.28, methanol:chloroform:acetic acid (5.94:1); MS m/e = 766(M+1), 758, 592, 562, 421, 346, 328.



Analysis for $C_{37}H_{46}ClN_5O_9 \cdot S \cdot 1.0 H_2O \cdot 1.0 CH_3COOH$ :			
Calculated:	C, 55.48;	H, 5.49;	N, 8.29
Found:	C, 55.42;	H, 5.33;	N, 8.77

## Example 8

(S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-(methoxycarbonyl)-benzoxazol-2-yl, A=CO, L=p-phenylene,  $R^4=R^5 \cdot S(O_2) \cdot NH \cdot CO \cdot$ ,  $R^5=4-ClC_6H_4$ ).

- a. (1S)-Benzyloxycarbonyl-L-valyl-N-{1-(hydroxy)-[5-(methoxycarbonyl)benzoxazol-2-yl]methyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl).

A stirred solution of the imide of Example 4b (5.47 g) and 4-carbomethoxy-2-aminophenyl (5.10 g) in dry ethanol (50 ml) was heated for 3 hr at 60° under nitrogen. The mixture was dissolved in ethyl acetate, washed (1N HCl, 1N NaOH three times, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was flash chromatographed, eluting with acetone:hexanes (30:70), to afford 2.210 g of the product, TLC,  $R_f=0.18$ , acetone:hexanes (35:65); MS, 649(M+41), 637(M+29), 611(M+3), 610(M+2), 609(M+1), 591, 501.

Analysis for $C_{32}H_{40}N_4O_8 \cdot 0.35 CH_3CO_2C_2H_5$ :			
Calculated:	C, 62.73;	H, 6.74;	N, 8.76
Found:	C, 62.71;	H, 6.73;	N, 8.67

- b. (S)-Benzyloxycarbonyl-L-valyl-N-[1-5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl).

t-Butanol (0.340 ml) was added to a solution of the product of Example 8a (2.70 g) and Dess-Martin periodinane (4.62 g) in dichloromethane (20 ml) and the solution stirred at room temperature for 22 hr. The resulting suspension was diluted with ethyl acetate and was washed (three portions of 1:1 saturated  $Na_2S_2O_3$ :saturated  $NaHCO_3$ , brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with acetone:hexane (25:75) to afford 2.20 g of solid; TLC,  $R_f=0.21$ , acetone:hexanes (30:70); MS, m/e = 635(M+29), 608(M+2), 607(M+1), 374, 331, 91.

Analysis for $C_{32}H_{38}N_4O_8 \cdot 0.50 H_2O$ :			
Calculated:	C, 62.43;	H, 6.38;	N, 9.10
Found:	C, 62.43;	H, 6.24;	N, 8.91

c. (S)-L-Valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula V, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl).

To a stirred solution of the product of Example 8b (500 mg) in dichloromethane (4 ml) under nitrogen was added trifluoromethanesulfonic acid (0.385 ml) dropwise. After 5 min the reaction mixture was poured into distilled water (100 ml) and was extracted three times with dichloromethane. The aqueous layer was adjusted to pH 8 with  $\text{NaHCO}_3$  and washed three times with dichloromethane. The aqueous phase was treated with 1N NaOH (50 ml) and washed once more with dichloromethane. The organic washes were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated to afford 185 mg (48%) of a white foam; TLC,  $R_f=0.22$ , methanol:chloroform (5:95).

d. (S)-[4-{(4-Chlorophenyl)sulfonylamino carbonyl}-benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene,  $R^1=R^5=\text{R}^6.\text{S}(\text{O}_2).\text{NH}.\text{CO}-$ ,  $R^2=4-\text{ClC}_6\text{H}_4$ ).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (160 mg) was added to a solution of the product of Example 8c (185 mg), 1-hydroxybenzotriazole (110 mg), and the product of Example 1 part c (280 mg) in tetrahydrofuran (3 ml) and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed (three times with 1N HCl, brine), dried ( $\text{MgSO}_4$ ), and evaporated. The crude product was purified by flash chromatography eluting with acetone:dichloromethane:acetic acid (20:80:1 drop/ml) to afford 160 mg of solid;  $R_f=0.38$ , methanol:chloroform:acetic acid (5:95:1 drop/ml); HPLC  $t_R=15.84$ , Col A, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1), FR=2; MS m/e=684(M+29), 656(M+1), 375, 374, 356, 355, 354, 352, 302, 283, 260, 259, 178, 168.

Analysis for $\text{C}_{38}\text{H}_{40}\text{ClN}_5\text{O}_{10}\text{S} \cdot 1.0 \text{ H}_2\text{O} \cdot 1.0 \text{ CH}_3\text{CO}_2\text{H}$ :			
Calculated:	C, 55.07;	H, 5.31;	N, 8.03
Found:	C, 55.05;	H, 5.13;	N, 8.06

#### Example 9

(S)-[4-{(4-Chlorophenyl)sulfonylamino carbonyl}benzoyl]-L-valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=6-(methoxycarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene,  $R^4=R^5.\text{S}(\text{O}_2).\text{NH}.\text{CO}-$ ,  $R^2=4-\text{ClC}_6\text{H}_4$ ).

a. (1S)-Benzyloxy carbonyl-L-valyl-N-[1-(hydroxy)-[6-(methoxycarbonyl)benzoxazol-2-yl]methyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=6-(methoxycarbonyl)benzoxazol-2-yl).

A stirred solution of imidate prepared as described in Example 4b (1.00 g) and 5-carbomethoxy-2-aminophenyl (930 mg) in dry ethanol (9 ml) was heated for 4 hr at  $60^\circ$  under nitrogen. The mixture was dissolved in ethyl acetate, washed (twice with 1N NaOH, brine), dried ( $\text{MgSO}_4$ ) and evaporated. The crude product was flash chromatographed, eluting with acetone:hexanes (35:65), to afford 300 mg of the product; TLC,  $R_f=0.50$ , acetone:hexanes (45:55), MS, m/e=610(M+2), 609(M+1).

b. (S)-Benzyloxycarbonyl-L-valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q = 6-(methoxycarbonyl)benzoxazol-2-yl).

t-Butanol (0.050 ml) was added to a solution of the product of Example 9a, (300 mg) and Dess-Martin periodinane (630 mg) in dichloromethane (3 ml) and the solution stirred at room temperature for 17 hr. The resulting suspension was diluted with ethyl acetate and was washed (three portions of 1:1 saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>:NaHCO<sub>3</sub>, brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified by flash chromatography, eluting with acetone:hexane (30:70), to afford a solid which was dissolved in acetonitrile (30 ml) and treated with 300 mg of activated charcoal. The mixture was stirred for 10 min, filtered and evaporated to afford 257 mg of the product; TLC, R<sub>f</sub> = 0.49, acetone:hexanes (40:60); MS, m/e = 635-(M+29), 608(M+2), 607(M+1).

Analysis for C <sub>32</sub> H <sub>38</sub> N <sub>4</sub> O <sub>8</sub> ·0.5 H <sub>2</sub> O:			
Calculated:	C, 62.43;	H, 6.38;	N, 9.10
Found:	C, 62.62;	H, 6.26;	N, 8.94

c. (S)-L-Valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide trifluoromethanesulfonic acid salt (Formula V, heterocycle containing X, N and Q = 6-(methoxycarbonyl)benzoxazol-2-yl).

To a stirred solution of the product of Example 9b, (210 mg) in dichloromethane (1.5 ml) under nitrogen was added trifluoromethane sulfonic acid (0.15 ml) dropwise. After 40 min the reaction mixture was evaporated. The resulting solid was placed under vacuum for an hour and used directly in Example 9d, below; TLC R<sub>f</sub> = 0.00 acetone:hexanes (25:75); MS, m/e = 244, 242, 235, 195, 189, 186, 161, 178, 121, 105, 93, 92, 91, 79.

d. (S)-[4-[(4-Chlorophenyl)sulfonylamino]carbonyl]-benzoyl]-L-valyl-N-[1-[6-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 6-(methoxycarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene, R<sup>1</sup> = R<sup>2</sup> S(O<sub>2</sub>).NH.CO-, R<sup>3</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg) was added to a solution of the product of Example 9c, above, 1-hydroxybenzotriazole (50 mg) and 4-[(4-chlorophenyl)sulfonylamino]benzoic acid (130 mg) in methylene chloride (2 ml) and tetrahydrofuran (2 ml) followed by the addition of 4-methylmorpholine (0.041 ml) and the solution stirred at room temperature for 16 hr. Additional 4-methylmorpholine (0.041 ml) was added to the reaction mixture and the reaction stirred an addition 7 hr. The reaction mixture was diluted with ethyl acetate, washed (1N HCl (three times), brine), dried (MgSO<sub>4</sub>), and evaporated. The crude product was purified by flash chromatography, eluting with acetone:methylene chloride:acetic acid (30:70:1), to afford a solid (160 mg) which was further purified by flash chromatography, using a gradient elution of acetone:methylene chloride:acetic acid (500 ml of 0:100:1; 900 ml of 10:90:1; then 50:50:1), to afford the title compound (71.6 mg); TLC, R<sub>f</sub> = 0.17, acetone:chloroform:acetic acid (10:90:1); HPLC, t<sub>R</sub> = 15.84, Col. A, FR = 2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS, m/e = 794(M+1), 778, 777, 776, 423, 422, 421, 384, 374, 357, 356, 355, 354, 259.

Analysis for C <sub>38</sub> H <sub>46</sub> ClN <sub>5</sub> O <sub>10</sub> S·1.0 H <sub>2</sub> O·1.5 CH <sub>3</sub> CO <sub>2</sub> H:			
Calculated:	C, 54.57;	H, 5.36;	N, 7.76.
Found:	C, 54.34;	H, 5.19;	N, 7.81.

## Example 10

(S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzo-  
 yl-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)carbonyl-2-  
 methylpropyl]-L-prolinamide (Formula I, heterocycle  
 containing X, N and Q=5-carboxybenzoxazol-2-yl, A=CO,  
 L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

a. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=5-carboxybenzoxazol-2-yl).

A stirred solution of imidate prepared as in Example 4b (3.00 g) and 3-amino-4-hydroxybenzoic acid (2.55 g) in dry ethanol (25 ml) was heated for 1.5 hr at 60° under nitrogen, after which time an additional amount of imidate (2.00 g) and amino phenol (1.85 g) were added. The mixture was heated an additional 8.25 hr. The mixture was dissolved in ethyl acetate, washed (1N HCl (twice), brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was flash chromatographed, eluting with acetone:hexanes:acetic acid (50:50:1), to afford the product (330 mg); TLC, R<sub>f</sub>=0.19, acetone:acetic acid (50:50:1); MS, m/e=595(M+1), 577.

b. (1S)-L-Valyl-N-[1-(5-carboxybenzoxazol-2-yl)-hydroxymethyl-2-methoxypropyl]-L-prolinamide (Formula XV, heterocycle containing X, N and Q=5-carboxybenzoxazol-2-yl).

A mixture of 10% palladium on carbon (1.50 g) and the product of Example 10a (2.90 g) in ethanol (100 ml) was hydrogenated in a shaker at 3.4 bar for 3 hr, after which time the mixture was filtered through diatomaceous earth and the solvent evaporated to afford product (1.95 g); TLC, R<sub>f</sub>=0.0, methanol:chloroform:acetic acid (5:95:1); MS, m/e=461(M+1), 443, 331, 319, 290, 265, 248, 232, 225, 198, 197, 196, 154.

c. (1S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)-hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q=5-carboxybenzoxazol-2-yl, A=CO, L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

Isobutyl chloroformate (0.34 ml) was added dropwise over the course of three min to a stirred, -40° solution of 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoic acid (850 mg) and 4-methylmorpholine (0.58 ml) in dry tetrahydrofuran (12 ml). The mixture was stirred for 30 min after which time the product from Example 10b (800 mg) in dimethylformamide (9 ml) was added dropwise to the reaction mixture. The reaction was allowed to warm slowly to room temperature overnight. The resulting mixture was diluted with ethyl acetate, washed (twice with 1N HCl, once with brine), dried (MgSO<sub>4</sub>), and evaporated. The crude material was flash chromatographed, eluting with acetone:methylene chloride:acetic acid (30:70:1), to afford the product (570 mg); TLC, R<sub>f</sub>=0.28, acetone:methylene chloride:acetic acid (42:60:1); MS, m/e=782-(M+1), 764, 423, 421, 377, 193, 191.

d. (S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-carboxybenzoxazol-2-yl)-carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-carboxybenzoxazol-2-yl, A=CO, L=p-phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

t-Butanol (0.070 ml) was added to a solution of the product of Example 10c (560 mg) and Dess-Martin periodinane (910 mg) in dry dichloromethane (3 ml) and the solution stirred at room temperature for 21 hr. The resulting suspension was diluted with ethyl acetate, washed (half saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (three times)), dried (MgSO<sub>4</sub>), and evaporated. The crude product was purified by flash chromatography, eluting with acetone:dichloromethane:acetic acid (30:70:1), to afford the title compound (100 mg); TLC, R<sub>f</sub>=0.28,

methanol:chloroform:acetic acid (5:95:1); MS, m/e = 781(M+1), 764, 763, 762, 423, 421, 342, 341; HPLC,  $t_R$  = 10.43, Col A, FR = 2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1).

Analysis for $C_{27}H_{38}ClN_3O_6S \cdot 0.50 H_2O \cdot 1.50 CH_3CO_2H$ :			
Calculated:	C, 54.64;	H, 5.16;	N, 7.96.
Found:	C, 54.64;	H, 5.30;	N, 7.73.

# Example 11

[4-(Isopropylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, A=CO, L=p-phenylene,  $R^4=R^5=S(O_2)$ ).NH.CO-,  $R^5=CH(CH_3)_2$ ).

## a. t-Butyl 4-(isopropylsulfonylaminocarbonyl)benzoate.

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (198 mg) was added to a stirred mixture of 4-(t-butoxycarbonyl)benzoic acid (195 mg), 2-propanesulfonamide (98 mg) and 4-dimethylaminopyridine (126 mg) in dichloromethane (3.7 ml). The mixture was stirred overnight, diluted with ethyl acetate, washed (1N HCl, brine), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography, eluting with acetone:hexanes (75:25), to afford the product (193 mg); TLC,  $R_f$  = 0.64, acetone:hexanes (75:25); MS, m/e = 356(M+29), 330(M+3), 329(M+2), 328(M+1), 272, 223, 222, 205, 204, 166.

## b. 4-(Isopropylsulfonylaminocarbonyl)benzoic acid.

Trifluoroacetic acid (5 ml) was added to the product from Example 11a (193 mg). The resulting solution was stirred 6.5 hr, then evaporated. The crude material product was redissolved in ether and evaporated (four times). The crude product was then added to a volume of hexanes and evaporated (twice) to afford the product (214 mg); TLC,  $R_f$  = 0.29, acetone:hexanes:acetic acid (50:50:1); MS, m/e = 272(M+1), 166, 148, 115, 109, 95.

## c. [4-(Isopropylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q=2-benzoxazolyl, $R^4=R^5=S(O_2)$ ).NH.CO-, $R^5=CH(CH_3)_2$ ).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (166 mg) was added to a stirred solution of the product of Example 1k (362 mg), the product of Example 11b (214 mg) and 1-hydroxybenzotriazole (117 mg) in dichloromethane (3 ml), and the mixture stirred overnight. The reaction mixture was diluted with ethyl acetate, washed (1N HCl (three times)), dried ( $MgSO_4$ ), and evaporated. The crude product was purified by flash chromatography, eluting with tetrahydrofuran:hexanes:acetic acid (65:35:1) to afford the product (215 mg); TLC,  $R_f$  = 0.44, acetone:hexanes:acetic acid (75:25:1); MS, m/e = 671(M+2), 670(M+1), 653, 652, 353, 319, 318, 300, 249, 231, 204, 124, 120.

## d. [4-(Isopropylsulfonylaminocarbonyl)benzoyl]-L-valyl-N-1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzoxazolyl, L=p-phenylene, $R^4=R^5=S(O_2)$ ).NH.CO-, $R^5=CH(CH_3)_2$ ).

Dess-Martin periodinane (408 mg) was added to a stirred solution of the product of Example 11c (215 mg) and t-butanol (0.09 ml) in dichloromethane (3 ml). The resulting suspension was stirred overnight. The reaction mixture was filtered and the solvent evaporated. The resulting oil was filtered through silica gel with acetone:hexanes (65:35) to afford 404 mg of the crude product. This crude product was purified by flash chromatography eluting with tetrahydrofuran:hexanes:acetic acid (55:45:1) and the resulting solid was dissolved in dichloromethane (5 ml) and treated with decolorizing carbon (15 mg). The suspension was filtered and the solvent evaporated to afford the product (130 mg); TLC,  $R_f$ =0.67, methanol:chloroform:acetic acid (5:95:1); HPLC,  $t_R$ =9.50, Col. B, FR=2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS,  $m/e$ =696(M+29), 669(M+2), 668-(M+1), 651, 650, 353, 317, 316, 309, 299, 298, 297, 296, 201.

Analysis for  $C_{23}H_{41}N_5O_5S \cdot 0.85 H_2O$ :

Calculated:	C, 58.02;	H, 6.30;	N, 10.25
Found:	C, 58.29;	H, 6.17;	N, 9.67

Example 12

[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(2-oxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-oxazolyl, A=CO, L=p-phenylene,  $R^4=R^5=S(O_2)$ .-NH.CO-,  $R^5=4-ClC_6H_4$ ).

## a. 2-Trimethylsilyl oxazole.

n-Butyllithium (28.5 ml of a 2.54 M solution in hexane) was added to a -78° solution of oxazole (5.0 g) in ether (150 ml). The resulting solution was stirred at -78° for 30 min, followed by the addition of trimethylsilyl chloride (7.86 g), and the mixture allowed to warm to room temperature. The reaction mixture was distilled and the fraction with a boiling point of about 130° was collected to afford 2-trimethylsilyl oxazole (5.12 g); MS,  $m/e$ =142(M+1), 91, 73.

## b. (1S)-Benzyloxycarbonyl-L-valyl-N-[1-(2-oxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=2-oxazolyl).

A solution of the aldehyde (of formula XI) prepared in a similar manner to that described in Example 1h (7.4 g) and the product of Example 12a (4.84 g) in toluene (10 ml) was heated at 80° for 24 hr and at 60° for an additional 14 hr. The solvents were evaporated, and the residue was dissolved in tetrahydrofuran (50 ml) and treated with 1N HCl (5 ml) and stirred for 30 min. The mixture was dissolved in ethyl acetate, washed (1N HCl, saturated sodium bicarbonate, brine), dried ( $MgSO_4$ ), and evaporated. The crude material was purified by flash chromatography, eluting with acetone:hexanes (30:70), to afford the product (4.57 g); TLC,  $R_f$ =0.31, methanol:chloroform (5:95); MS,  $m/e$ =501(M+1), 483, 393.

Analysis for  $C_{28}H_{35}NO_6$ :

Calculated:	C, 62.36;	H, 7.25;	N, 11.19
Found:	C, 62.52;	H, 7.22;	N, 10.87

c. (S)-Benzyloxycarbonyl-L-valyl-N-[2-methyl-1-[(2-oxazolyl)carbonyl]propyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q = 2-oxazolyl).

t-Butanol (0.83 ml) was added to a solution of the product of Example 12b (4.4 g) and Dess-Martin periodinane (15 g) in dichloromethane (150 ml) and stirred for 18 hr. The resulting suspension was partitioned between saturated  $\text{Na}_2\text{S}_2\text{O}_3$ :saturated  $\text{NaHCO}_3$  (1:1) and ethyl acetate. The ethyl acetate solution was washed (saturated  $\text{Na}_2\text{S}_2\text{O}_3$ :saturated  $\text{NaHCO}_3$  (1:1), saturated  $\text{NaHCO}_3$ , brine), dried ( $\text{MgSO}_4$ ), and evaporated. The residue was purified by flash chromatography, eluting with acetone:hexanes (35:65), to afford 4.8 g solid. This solid was dissolved in ethyl acetate, washed (saturated  $\text{Na}_2\text{S}_2\text{O}_3$ :saturated  $\text{NaHCO}_3$  (1:1), saturated  $\text{NaHCO}_3$ , brine), dried ( $\text{MgSO}_4$ ), and evaporated to afford the product as a white foam (3.74 g); TLC,  $R_f$  = 0.32, acetone:hexanes (40:60); MS,  $m/e$  = 499 (M + 1), 266.

Analysis for $\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}_6$ :			
Calculated:	C, 62.64;	H, 6.87;	N, 11.24
Found:	C, 62.30;	H, 6.74;	N, 11.01

d. [4-(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl-L-valyl-N-[1-(2-oxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-oxazolyl, L = p-phenylene,  $R^1 = R^2 = \text{S}(\text{O}_2)\text{NH}-\text{CO}-$ ,  $R^3 = 4-\text{ClC}_6\text{H}_4$ ).

Trifluoromethanesulphonic acid (0.89 ml) was added to a solution of the product of Example 12c (1.0 g) in dichloromethane (15 ml) and stirred for 10 min, the solvents evaporated and the residue placed under high vacuum for 20 min. The residue was dissolved in tetrahydrofuran (40 ml) and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (429 mg), 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoic acid (800 mg) and 4-dimethylaminopyridine (1.97 g). The mixture was stirred at room temperature for 16 hr, dissolved in ethyl acetate, washed (1N HCl, saturated  $\text{NaHCO}_3$ , brine), dried ( $\text{MgSO}_4$ ), and evaporated. The crude material was purified by flash chromatography, eluting with acetone:hexanes:acetic acid (10:90:1 to 20:80:1), to afford the product (930 mg); TLC,  $R_f$  = 0.40, methanol:chloroform:acetic acid (5:95:1); HPLC,  $t_R$  = 7.35, Col A, FR = 2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS,  $m/e$  = 686 (M + 1), 668, 393, 377, 266, 248.

Analysis for $\text{C}_{32}\text{H}_{36}\text{ClN}_5\text{O}_6\text{S} \cdot 0.5 \text{H}_2\text{O} \cdot 0.1 \text{CH}_3\text{COOH}$ :			
Calculated:	C, 54.07;	H, 5.47;	N, 9.27.
Found:	C, 53.78;	H, 5.33;	N, 9.25.

## Example 13

5 [4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-  
 L-valyl-N-[1-(2-benzothiazolyl)carbonyl-2-methyl-  
 propyl]-L-prolinamide (Formula I, heterocycle con-  
 10 taining X, N and Q=2-benzothiazolyl, A=CO, L=P-  
 phenylene,  $R^4=R^5.S(O_2).NH.CO-$ ,  $R^5=4-ClC_6H_4$ ).

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## 15 a. Nα-Benzoyloxycarbonyl-N-methoxy-N-methylvalinamide.

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (19.07 g) in dichloromethane (500 ml) was cooled to -10°. To this solution were added 1-hydroxybenzotriazole (13.44 g) and 4-methylmorpholine (11.5 ml). A solution of N-(benzyloxycarbonyl)-L-valine (25.0 g) in dichloromethane (200 ml) was added dropwise to the reaction mixture. After addition was complete, the mixture was warmed to ambient temperature and stirred for 0.5 hr before being cooled to 10°. A mixture of N-methyl-O-methylhydroxylamine hydrochloride (9.7 g) and 4-methylmorpholine (11.5 ml) in dichloromethane (150 ml) was added dropwise to the stirred reaction mixture. The reaction was warmed to ambient temperature with overnight stirring. The mixture was evaporated and the residue was partitioned between water and ethyl acetate. The organic layer was washed (10% HCl, saturated NaHCO<sub>3</sub>, brine), dried (MgSO<sub>4</sub>), evaporated and dried overnight under high vacuum to give the product as a gum (26.25 g) which solidified in the freezer; TLC, R<sub>f</sub>=0.57, chloroform:methanol (40:1); MS, m/e=295(M+1), 234, 187, 162, 152, 119.

## 30 b. (S)-1-(2-Benzothiazolyl)-2-(benzyloxycarbonyl)amino-3-methyl-1-butanone.

Dry ether (5 ml) was cooled to -78° and n-butyllithium (6.0 ml of 2.54 M solution in hexanes) was added. A dry ether (15 ml) solution of benzothiazole (1.83 g) was added rapidly dropwise. Stirring at -78° was continued for 10 min. An ether (10 ml) solution of amide prepared according to the procedure of Example 13a and used without further purification (2.00 g) was added via cannula, and the reaction mixture was allowed to warm to 30° with stirring for 1 hr. The reaction mixture was quenched by pouring into saturation NH<sub>4</sub>Cl and extracted with ethyl acetate. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a yellow oil (0.98 g); TLC, R<sub>f</sub>=0.67, hexane:ethyl acetate (2:1); MS, m/e=368(M+1), 206, 191, 162, 135, 91 (base).

## 40 c. 2-Amino-1-(2-benzothiazolyl)-3-methyl-1-butanone.

Material prepared according to the procedure of Example 13b (0.94 g) was dissolved in a mixture of dichloromethane (20 ml) and anisole (1 ml) under nitrogen. Trifluoromethanesulfonic acid (1 ml) was added and the reaction was stirred for 10 min. The reaction was diluted with dichloromethane and extracted with water. The aqueous extracts were washed with dichloromethane, brought to pH=8 with saturated NaHCO<sub>3</sub> and extracted with dichloromethane. The organic solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a yellow oil (0.50 g); TLC, R<sub>f</sub>=0.36, hexane:ethyl acetate (2:1).

## 50 d. Benzyloxycarbonyl-L-valyl-N-[1-(2-benzothiazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q=2-benzothiazolyl).

A dichloromethane solution of material prepared according to the procedure of Example 13c and used without further purification (0.5 g), 1-hydroxybenzotriazole (0.58 g) and product prepared according to the method of Example 11 (0.74 g) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.47 g), and the reaction mixture was stirred under nitrogen for 15 hr. The reaction mixture was diluted with dichloromethane, washed (saturated NaHCO<sub>3</sub>, 10% HCl), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a yellow oil (1.48 g); TLC, R<sub>f</sub>=0.39, chloroform:methanol (50:1); MS, m/e=585(M+1, base), 332, 331.



e. L-Valyl-N-[(2-benzothiazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula V, heterocycle containing X, N and Q=2-benzothiazolyl).

Amide prepared according to the procedure of Example 13d and used without further purification (1.20 g) was deprotected using a similar procedure to the procedure of Example 13c to give the product as an oil (0.34 g, 37%); TLC,  $R_f$  = 0.34, chloroform: methanol (10:1).

f. [4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[(2-benzothiazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-benzothiazolyl, A=CO, L=p-phenylene,  $R^4 = R^5 = S(O_2)$ ,  $NH.CO-$ ,  $R^3 = 4-ClC_6H_4$ ).

Amine prepared according to the procedure of Example 13e and used without further purification (0.34 g), 1-hydroxybenzotriazole (0.21 g) and 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoic acid (0.27 g) were combined in dichloromethane (12 ml) and the suspension was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17 g). Stirring was continued for 7.5 hr. The reaction was diluted with ethyl acetate and washed (saturated  $NaHCO_3$ , 10% HCl), dried ( $Na_2SO_4$ ) and evaporated to give an oily foam. Purification by flash chromatography, eluting with hexanes:ethyl acetate:acetic acid (50:50:1.5), gave the product as a white solid (0.32 g); TLC,  $R_f$  = 0.29, hexanes:ethyl acetate:acetic acid (50:50:1.5); HPLC,  $t_R$  = 26, Col A, FR = 2, water:acetonitrile:tetrahydrofuran:trifluoro acetic acid (55:35:15:0.1); MS,  $m/e$  = 752- (M+1), 423, 421, 393, 377, 342, 332, 315, 314 (base), 313, 312, 136.

Analysis for $C_{35}H_{38}ClN_5O_7S_2 \cdot 0.3 CH_3 COOH$ :			
Calculated:	C, 57.07;	H, 5.13;	N, 9.09
Found:	C, 57.32;	H, 5.45;	N, 8.76

#### Example 14

(S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=2-thiazolyl, A=CO, L=p-phenylene,  $R^4 = R^5 = S(O_2)$ ,  $NH.CO-$ ,  $R^3 = 4-ClC_6H_4$ ).

a. (S)-2-(Benzyloxycarbonyl)amino-3-methyl-1-(2-thiazolyl)-1-butanone.

To a cooled (-35°) solution of thiazole (1.23 ml) in dry tetrahydrofuran (40 ml) was added n-butyllithium (6.6 ml of a 2.18M solution in hexane) over 3 min. The dark brown reaction mixture was stirred in the temperature range -30° to -25° for 10 min. A solution of material prepared according to the procedure of Example 13a and used without further purification (1.7 g) in dry tetrahydrofuran (15 ml) was added rapidly over 1 min. Stirring at -30° was continued for 15 min. The mixture was quenched by pouring it into saturated  $NH_4Cl$  (100 ml), and the organics were extracted into ethyl acetate. The extracts were washed (saturated  $NaHCO_3$ ), dried ( $Na_2SO_4$ ) and evaporated to give a brown oil. Purification by flash column chromatography, eluting with hexane:ethyl acetate (2:1), gave the product as a yellow oil (1.81 g, 98%); TLC,  $R_f$  = 0.45, hexane:ethyl acetate (2:1); MS,  $m/e$  = 319(M+1, base), 275.

b. (S)-2-Amino-3-methyl-1-(2-thiazolyl)-1-butanone.

Ketone prepared according to the procedure of Example 14a (1.8 g) was dissolved in dichloromethane (30 ml) and treated with trifluoromethanesulfonic acid (2.5 ml) in a single portion, and the reaction was

stirred at ambient temperature for 5 min. The mixture was diluted with dichloromethane and extracted with water. The aqueous phase was brought to basic pH with saturation  $\text{NaHCO}_3$  and then was extracted with dichloromethane. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give the product as a dark yellow oil (0.78 g, 75%); TLC,  $R_f = 0.7$ , chloroform:methanol (10:1); MS,  $m/e = 185(\text{M}+1, \text{base})$ , 167, 140.

c. (S)-Benzyloxycarbonyl-L-valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide (Formula VI, heterocycle containing X, N and Q = 2-thiazolyl).

Amino ketone prepared according to the procedure of Example 14b (0.73 g) was dissolved in dichloromethane (25 ml). Sequentially added to the solution were benzyloxycarbonyl-L-valyl-L-proline (1.38 g), 1-hydroxybenzotriazole (1.07 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.76 g). The mixture was stirred overnight at ambient temperature under nitrogen. The reaction mixture was diluted with dichloromethane, washed (saturated  $\text{NaHCO}_3$ , 10% HCl), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give a yellow oil (2.5 g). Purification by flash chromatography, eluting with hexane:ethyl acetate (1:1) gave the product as a solid foam (1.61 g); TLC,  $R_f = 0.3$ , hexane:ethyl acetate (1:1); MS,  $m/e = 515(\text{M}+1, \text{base})$ , 407, 331, 282, 91.

Analysis for $\text{C}_{25}\text{H}_{34}\text{N}_4\text{O}_5 \cdot 0.5 \text{H}_2\text{O}$ :			
Calculated:	C, 59.64;	H, 6.74;	N, 10.70
Found:	C, 59.56;	H, 6.54;	N, 10.42

d. (S)-L-Valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide trifluoromethanesulfonic acid salt (Formula V, heterocycle containing X, N and Q = 2-thiazolyl).

Ketone prepared according to Example 14c (0.51 g) was dissolved in dichloromethane (15 ml) and was treated with trifluoromethanesulfonic acid (0.44 ml) in a single portion. The reaction mixture was stirred at ambient temperature for 15 min. Evaporation and drying under high vacuum gave a white gum (1.17 g, more than 100%). The weight of crude product in excess to 100% yield was assumed to be trifluoromethanesulfonic acid.

e. (S)-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]-benzoyl]-L-valyl-N-[2-methyl-1-(2-thiazolyl)carbonylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-thiazolyl, A = CO, L = p-phenylene,  $\text{R}^1 = \text{R}^2 = (\text{SO}_2)\text{NH}\cdot\text{CO}\cdot$ ,  $\text{R}^5 = 4\text{-ClC}_6\text{H}_4$ ).

Crude amino ketone prepared according to the procedure of Example 14d and used without further purification (1.14 g), 1-hydroxybenzotriazole (0.13 g), 4-[(4-chlorophenyl)sulfonylaminocarbonyl]benzoic acid (0.34 g) and 4-methylmorpholine (0.59 ml) were dissolved in tetrahydrofuran and the mixture was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The mixture was stirred overnight under nitrogen. Evaporation gave a residue which was partitioned between water and ethyl acetate. The organic phase was washed (10% HCl, water, brine), dried ( $\text{MgSO}_4$ ) and evaporated. Flash chromatography, eluting with chloroform:methanol:acetic acid (100:2.5:0.5), gave the product as a white foam (0.50 g). A second purification (same solvent system as above) yielded the title product as a white foam (0.43 g); TLC,  $R_f = 0.35$ , chloroform:methanol:acetic acid (100:2.5:0.5); MS,  $m/e = 702$  ( $^{25}\text{Cl}\cdot\text{M}+1$ ), 283, 262 (base), 120; HPLC,  $t_R = 8.54$ , Col A, FR = 2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1).

## Example 15

(S)-[4-[N'-(Phenylsulfonyl)ureido]benzoyl]-L-valyl-  
 N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolin-  
 amide (Formula I, heterocycle containing X, N and  
 Q=2-benzoxazolyl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).-  
 NH.CO.NR<sup>6</sup>-, R<sup>5</sup>=C<sub>6</sub>H<sub>5</sub>, R<sup>6</sup>=H).

a. 4-[N'-(Phenylsulfonyl)ureido]benzoic acid.

To a stirred solution of p-aminobenzoic acid (3.48 g) and 4-methylmorpholine (2.75 ml) in distilled tetrahydrofuran (110 ml) was added phenylsulfonyl isocyanate (4.65 g). The reaction mixture, which warmed slightly upon addition, was stirred for 18 hr, diluted with 1N HCl, and extracted with methylene chloride. The organic extracts were washed (1N HCl (twice), brine), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to afford a yellowish solid. This solid was triturated with ether and filtered to afford the product as a white solid (5.26 g, 65%); TLC, R<sub>f</sub>=0.25, methanol:chloroform:acetic acid (5:95:1); MS, 321(M+1), 303, 277, 257, 184, 164, 160, 159, 158, 141, 140, 139, 138, 137, 120, 94.

b. (1S)-Benzoyloxycarbonyl-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XIV, heterocycle containing X, N and Q=2-benzoxazolyl).

To a stirred solution of ethanol (42.3 ml) in chloroform (44 ml) at 0° was added dropwise acetyl chloride (46.5 ml) over 25 min. The mixture was stirred an additional 10 min. Cyanohydrin prepared as described in Example 4a (10.0 g), was added to the mixture, followed by an additional volume of chloroform (44 ml). The reaction mixture was stirred at 0° for 3 hr and the solvents evaporated to afford a white foam which was dissolved in ethanol (100 ml). To this ethanolic solution was added 2-aminophenol (7.14 g), and the resulting brown mixture was heated to 60° with stirring under nitrogen for 45 min. The reaction mixture was cooled, diluted with ether, washed (1N NaOH (5 times), brine), dried (Na<sub>2</sub>SO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub> (2:1 w/v)), and evaporated to obtain a brown foam (10.3 g). The crude material was purified by flash chromatography, eluting with acetone:hexanes (35:65), to afford the product (4.92 g); TLC, R<sub>f</sub>=0.24, methanol: chloroform (5:95); MS, m/e = 551(M+1), 331, 148, 108, 91.

Analysis for C<sub>39</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub> 0.50 H<sub>2</sub>O:

Calculated:	C, 64.39;	H, 7.02;	N, 10.01
Found:	C, 64.29;	H, 6.87;	N, 9.86

c. (1S)-L-Valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula XV, heterocycle containing X, N and Q=2-benzoxazolyl).

A mixture of 10% (w/w) palladium on carbon (800 mg, 50% (w/w) water wet) and the product from Example 15b (4.90 g) in ethanol (250 ml) was hydrogenated in a shaker at 3.4 bar from 2 hr, after which time an additional portion of catalyst (0.500 g) was added. The mixture was hydrogenated in a shaker at 3.4 bar for an additional 2 hr, filtered through diatomaceous earth and evaporated to afford the product as a solid (3.67 g, 99%); TLC, R<sub>f</sub>=0.42, methanol:chloroform (5:95); MS, m/e = 445(M+29), 418(M+2), 417-(M+1).

d. (1S)-[4-[N'-(Phenylsulfonyl)ureido]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N, and Q=2-benzoxazolyl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, R<sup>5</sup>=C<sub>6</sub>H<sub>5</sub>, R<sup>6</sup>=H).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg) was added to a solution of the product of Example 15c (380 mg), 1-hydroxybenzotriazole (140 mg), and 4-[N-(phenylsulfonyl)ureido]benzoic acid (320 mg) in dimethylformamide (5 ml) and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed (1N HCl (three times), brine), dried (MgSO<sub>4</sub>), and evaporated. The crude product was flash chromatographed, eluting with ethyl acetate:chloroform:acetic acid (50:50:1) to afford the product as a solid (460 mg); TLC, R<sub>f</sub> = 0.14, methanol:chloroform:acetic acid (5:95:1).

Analysis for C <sub>26</sub> H <sub>24</sub> N <sub>6</sub> O <sub>8</sub> S.1.0 H <sub>2</sub> O.1.0 CH <sub>3</sub> CO <sub>2</sub> H:			
Calculated:	C, 57.13;	H, 6.31;	N, 10.51.
Found:	C, 58.39;	H, 6.33;	N, 9.95.

e. (S)-[4-[N-(Phenylsulfonyl)ureido]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = p-phenylene, R<sup>4</sup> = R<sup>5</sup>, S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, R<sup>5</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>6</sup> = H).

Dess-Martin periodinane (440 mg) was added to a solution of t-butanol (0.048 ml) and the product of Example 15d (370 mg) in dry methylene chloride (2.5 ml). The mixture immediately darkened and was allowed to stir for 22 hr. The resulting suspension was diluted with methylene chloride, washed (1:1 (v/v) saturated sodium thiosulfate/sodium bicarbonate (3 times), brine), dried (MgSO<sub>4</sub>), and evaporated to afford 450 mg of crude oil. This was flash chromatographed, eluting with ethyl acetate:chloroform:acetic acid (50:50:1), then rechromatographed using the same system to afford the title compound (91 mg); TLC, R<sub>f</sub> = 0.22, ethyl acetate:chloroform:acetic acid (50:50:1); HPLC, t<sub>R</sub> = 8.46, Col B, FR = 2, water: acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS, m/e = 640, 317, 316, 298, 245, 219, 197, 120.

Analysis for C <sub>26</sub> H <sub>24</sub> N <sub>6</sub> O <sub>8</sub> S.1.0 H <sub>2</sub> O.2.0 CH <sub>3</sub> CO <sub>2</sub> H:			
Calculated:	C, 56.20;	H, 5.89;	N, 9.83.
Found:	C, 56.08;	H, 5.93;	N, 9.33.

#### Example 16

(S)-[4-[N'-(4-Chlorophenyl)sulfonyl]ureido]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = p-phenylene, R<sup>4</sup> = R<sup>5</sup>, S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, R<sup>5</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>, R<sup>6</sup> = H).

a. 4-[N'-(4-Chlorophenyl)sulfonyl]ureido]benzoic acid.

To a stirred solution of p-aminobenzoic acid (2.68 g) and 4-methylmorpholine (2.15 ml) in distilled tetrahydrofuran (90 ml) was added chlorophenylsulfonyl isocyanate (4.25 g). The reaction mixture, which warmed slightly upon addition, was stirred for 18 hr. The reaction mixture was acidified with 1N HCl, and a flocculent precipitate formed. The mixture was extracted with methylene chloride, leaving much of the precipitate. Evaporating the methylene chloride solution and triturating the resulting solid with ether afforded 1.25 g of a white solid. The original solid precipitate was lixiviated with methanol, and the resulting solution was evaporated to afford a white solid which was triturated with ether to afford an additional 4.90 g (total

yield 5.15 g, 89%) of white solid; TLC,  $R_f = 0.21$ , methanol:chloroform:acetic acid (5:95:1), MS,  $m/e = 355$  ( $M+1$ ), 220, 219, 218, 192, 177, 175, 164, 138, 138, 120, 94.

- b. (1S)-[4-[N-{(4-Chlorophenyl)sulfonyl}ureido]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)hydroxymethyl]-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = p-phenylene,  $R^1 = R^2$ ,  $S(O_2).NH.CO.NR^3$ ,  $R^3 = 4-ClC_6H_4$ ,  $R^4 = H$ ).

1-(3-Dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (210 mg) was added to a solution of the product of Example 15c (360 mg), 4-dimethylaminopyridine (130 mg), and 4-[N-{(4-chlorophenyl)sulfonyl}ureido]benzoic acid (507 mg) in tetrahydrofuran (5 ml); and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed (distilled water (3 times), 1N HCl, saturated sodium bicarbonate, brine). The bicarbonate wash was acidified to pH = 1 and washed three times with ethyl acetate. The combined organic phases were washed (brine), dried ( $Na_2SO_4$ ), and evaporated. The crude product was flash chromatographed, eluting with tetrahydrofuran:chloroform:acetic acid (70:30:1). The resulting material was filtered through silica gel using tetrahydrofuran: chloroform:acetic acid (30:70:1 to 100:0:1) to afford the product (350 mg) as a solid; TLC,  $R_f = 0.55$ , tetrahydrofuran:chloroform:acetic acid (80:20:1); MS,  $m/e = 247$ , 197, 163.

Analysis for  $C_{27}H_{41}ClN_4O_5S.4.0. H_2O.0.50 CH_3CO_2H$ :

Calculated:	C, 48.94;	H, 6.03;	N, 7.29
Found:	C, 48.64;	H, 5.16;	N, 7.53

- c. (S)-[4-[N-{(4-Chlorophenyl)sulfonyl}ureido]benzoyl]-L-valyl-N-[1-(2-benzoxazolyl)carbonyl]-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 2-benzoxazolyl, A = CO, L = p-phenylene,  $R^1 = R^2$ ,  $S(O_2).NH.CO.NR^3$ ,  $R^3 = 4-ClC_6H_4$ ,  $R^4 = H$ ).

Dess-Martin periodinane (500 mg), was added to a solution of t-butanol (0.055 ml) and the product from Example 15b (440 mg) in dry methylene chloride (3 ml). The mixture immediately darkened and was allowed to stir for 22 hr. The resulting suspension was diluted with ethyl acetate, washed (1:1 (v/v) saturated sodium thiosulfate:sodium bicarbonate (3 times)), dried ( $MgSO_4$ ), and evaporated to afford 570 mg of an oil. This was flash chromatographed, eluting with acetone:methylene chloride:acetic acid (60:40:1), to afford the title compound (95 mg). TLC,  $R_f = 0.50$ , methanol:chloroform:acetic acid (10:90:1); HPLC,  $t_R = 14.68$ , Col B, FR = 2, water:acetonitrile: tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS,  $m/e = 317$ , 316, 219, 192, 120.

Analysis for  $C_{25}H_{39}ClN_4O_5S.1.0 CH_3CO_2H$ :

Calculated:	C, 56.26;	H, 5.34;	N, 10.36
Found:	C, 56.23;	H, 5.50;	N, 10.59

## Example 17

(S)-[4-{N'-[(4-Chlorophenyl)sulfonyl]ureido]benzoyl]-  
 L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]car-  
 bonyl-2-methylpropyl]-L-prolinamide (Formula I,  
 heterocycle containing X, N and Q=5-(methoxycarbonyl)-  
 benzoxazol-2-yl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).NH.-  
 CO.NR<sup>6</sup>, R<sup>5</sup>=4-ClC<sub>6</sub>H<sub>4</sub>, R<sup>6</sup>=H).

a. (S)-L-Valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula V, heterocycle containing X, N, and Q=5-(methoxycarbonyl)benzoxazol-2-yl).

To a stirred solution of the product of Example 8b (1.00 mg) in methylene chloride (8 ml) under nitrogen was added dropwise trifluoromethanesulfonic acid (0.73 ml). After 10 min the reaction mixture was diluted with dichloromethane and washed three times with distilled water. The pH of the resulting solution was adjusted to pH 8 by the addition of a solution of saturated sodium bicarbonate (25 ml). The basic solution was vigorously extracted with dichloromethane six times. Sodium chloride (10 g) was added to the remaining aqueous layer, and it was extracted twice with dichloromethane. All the organic extracts were combined, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to afford the product (620 mg); TLC, R<sub>f</sub>=0.20, methanol:chloroform, (5:95).

b. (S)-[4-{N'-[(4-Chlorophenyl)sulfonyl]ureido]benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>, R<sup>5</sup>=4-ClC<sub>6</sub>H<sub>4</sub>, R<sup>6</sup>=H).

1-(3-Dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (100 mg), was added to a solution of the product of Example 17a (225 mg), 1-hydroxybenzotriazole (70 mg), and 4-[N'-[(4-chlorophenyl)sulfonyl]ureido]benzoic acid (190 mg) in dichloromethane (3 ml) and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed (1N HCl (3 times), brine), dried (MgSO<sub>4</sub>), and evaporated. The crude product was purified by flash chromatography, eluting with acetone:methylene chloride:acetic acid (10:90:1), to afford the title compound (271 mg) as a solid; TLC, R<sub>f</sub>=0.14, acetone:dichloromethane:acetic acid (20:80:1); HPLC, t<sub>R</sub>=13.47, Col A, FR=2, water:acetonitrile:tetrahydrofuran:trifluoroacetic acid (55:35:15:0.1); MS, m/e=699, 374, 245, 219, 197, 178, 120.

Analysis for C<sub>38</sub>H<sub>44</sub>ClN<sub>6</sub>O<sub>10</sub>S<sub>3.7</sub>H<sub>2</sub>O.0.70 CH<sub>3</sub>CO<sub>2</sub>H:

Calculated:	C, 51.55;	H, 5.62;	N, 9.15
Found:	C, 51.40;	H, 4.97;	N, 9.48

## Example 18

4-[(Trifluoromethylsulfonyl)amino]benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q=5-(methoxycarbonyl)benzoxazol-2-yl, A=CO, L=p-phenylene, R<sup>4</sup>=CF<sub>3</sub>.S(O<sub>2</sub>).NH-).

## a. Ethyl 4-[(trifluoromethylsulfonyl)amino]benzoate.

Trifluoromethanesulfonic anhydride (4.1 ml) was added dropwise to a precooled (0°) solution of ethyl p-aminobenzoate (3.3 g) in dichloromethane (50 ml) under nitrogen. The reaction mixture was stirred for 1 hr at 0°, then was allowed to warm to room temperature and was stirred for 1 hr. After the reaction mixture was evaporated, ethyl acetate (125 ml) was added to the residue; and the resultant organic solution was washed (1N HCl, then brine), dried (MgSO<sub>4</sub>), and evaporated. The residue was purified by flash chromatography, eluting with chloroform:methanol (95:5), to give the product as a white powder (1.27 g); TLC, R<sub>f</sub> = 0.37, chloroform:methanol (90:10).

## b. 4-[(Trifluoromethylsulfonyl)amino]benzoic acid.

A solution of 1N NaOH (8.4 ml) was added to a stirred solution of the product of Example 18a (1.25 g) in methanol (25 ml). Water (2 ml) was added, and the reaction mixture was stirred overnight. After the methanol was distilled off under water aspiration vacuum, the resulting aqueous residue was diluted with water (20 ml). The aqueous solution was washed with ethyl acetate, made acidic (pH 2) with 1N HCl, and extracted with ethyl acetate (total = 40 ml). The organic phase was dried (MgSO<sub>4</sub>) and evaporated to give the product as a white powder (1.05 g); TLC, R<sub>f</sub> = 0.4, chloroform:methanol:acetic acid (98:4:0.2).

## c. (S)-L-Valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula V, heterocycle containing X, N, and Q = 5-(methoxycarbonyl)benzoxazol-2-yl).

To a stirred solution of the product of Example 8b (750 mg) in methylene chloride (5 ml) under nitrogen was added dropwise trifluoromethanesulfonic acid (0.53 ml). After 20 min the reaction mixture was diluted with dichloromethane and washed three times with distilled water. Sodium chloride (5 g) was added to the combined aqueous layers and the resulting solution was adjusted to pH 8 by the addition of a solution of saturated sodium bicarbonate (20 ml). The basic solution was vigorously extracted with dichloromethane eight times. The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to afford the product (420 mg); TLC, R<sub>f</sub> = 0.28, methanol:chloroform (5:95).

d. [4-{(Trifluoromethylsulfonyl)amino}benzoyl]-L-valyl-N-[1-[5-(methoxycarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 5-(methoxycarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene, R<sup>1</sup> = CF<sub>3</sub>.S(O)<sub>2</sub>.NH<sub>2</sub>).

1-[3-Dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (240 mg) was added to a solution of the product of Example 18c (420 mg), 4-dimethylaminopyridine (110 mg), and 4-[(trifluoromethylsulfonyl)amino]benzoic acid (340 mg) in tetrahydrofuran (3 ml); and the solution stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate, washed (1N HCl (3 times), brine), dried (MgSO<sub>4</sub>), and evaporated. The crude product was purified by flash chromatography, eluting with methanol:chloroform:acetic acid (20:80:1), to afford the title compound (330 mg) as a solid; TLC R<sub>f</sub> = 0.50, methanol:chloroform:acetic acid (5:95:1); HPLC, t<sub>R</sub> = 15.61, Col A, water:acetonitrile:tetrahydrofuran:acetic acid (55:35:15:0.1), FR = 2; MS, m/e = 752(M + 29), 724(M + 1), 706, 374, 356, 351, 323.

Analysis for C<sub>32</sub>H<sub>36</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S.0.60 H<sub>2</sub>O.0.80 CH<sub>3</sub>CO<sub>2</sub>H:

Calculated:	C, 51.57;	H, 5.20;	N, 8.95.
Found:	C, 51.29;	H, 5.07;	N, 8.97.

## Example 19

S-[4-[(4-Chlorophenyl)sulfonylaminocarbonyl]benzoyl]-  
 L-valyl-L-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]car-  
 bonyl-2-methylpropyl]-L-prolinamide (Formula I,  
 heterocycle containing X, N and Q=5-(aminocarbonyl)-  
 benzoxazol-2-yl, A=CO, L=p-phenylene, R<sup>4</sup>=R<sup>5</sup>.S(O<sub>2</sub>).-  
 NH.CO-, R<sup>5</sup>=4-ClC<sub>6</sub>H<sub>4</sub>).

## Method A

Material prepared as described in Example 6 and estimated to contain at least 95% of the (S)-  
 diastereomer (200 mg) was dissolved in hot chloroform (15 ml), filtered, and diluted to a total volume of 25  
 ml with hot chloroform. Toluene (5 ml) was added until the solution just turned cloudy and a few drops of  
 chloroform were added resulting in a clear solution. The solution was allowed to cool slowly. After 4 days,  
 the supernatant was removed by filtration and the crystallized solid was dried under nitrogen to afford 101  
 mg white solid; mp 165-180°;  $[\alpha]_D^{25} = -73.2^\circ$  (c=2.5, CH<sub>3</sub>OH).

## Method B

a. Benzylloxycarbonyl-L-valyl-L-proline t-butyl ester.

N-Benzylloxycarbonyl-L-valine (121.3 g), 1-hydroxybenzotriazole (130.5 g) and dry dimethylformamide  
 (DMF) (800 ml) were placed in a 5 liter, 3-necked flask equipped with a mechanical stirrer, thermometer,  
 and a calcium sulfate drying tube, under nitrogen atmosphere. The mixture was cooled to 0° for 15 min  
 and proline t-butyl ester (82.6 g) in dry DMF (800 ml) was added at a fast dropwise rate over 2 h while the  
 temperature of the reaction mixture was maintained at 0°. Dicyclohexylcarbodiimide (109.4 g) in dry DMF  
 (400 ml) then was added in one portion to the reaction mixture. The reaction was stirred at 0° for 3 h,  
 allowed to warm to room temperature gradually over 1 h, and stirred for 48 h, whereupon the reaction was  
 shown to be complete by TLC [R<sub>f</sub>=0.55, chloroform:ethyl acetate (85:15)]. The reaction mixture was chilled  
 in ice/water and filtered cold to remove the precipitated dicyclohexyl urea. The DMF was evaporated using  
 a mechanical vacuum pump and at a maximum bath temperature of 40°. The remaining oil was diluted with  
 ethyl acetate (2 liter), chilled, and refiltered to remove additional dicyclohexyl urea. The ethyl acetate  
 solution was washed (20% (w/v) citric acid solution (twice), saturated sodium chloride solution, saturated  
 sodium bicarbonate solution (twice), and saturated sodium chloride solution), dried (MgSO<sub>4</sub>), and evap-  
 orated to afford crude benzylloxycarbonyl-L-valyl-L-proline t-butyl ester as an amber oil (208.3 g, 100%).

b. L-Valyl-proline t-butyl ester.

A solution of benzylloxycarbonyl-L-valyl-L-proline t-butyl ester (51.8 g) dissolved in absolute ethanol (1  
 liter) was placed in a 2 liter hydrogenation bottle. The reaction mixture was purged with nitrogen, and 10%  
 (w/w) palladium on carbon catalyst (10 g, 50% (w/w) water wet) was added. The reaction was placed on a  
 large shaker apparatus and shaken at room temperature under a hydrogen atmosphere (3.4 bar). After 1 h,  
 hydrogen uptake ceased. The reaction mixture was checked by TLC [chloroform:ethyl acetate (85:15)] and  
 shown to contain considerable starting material (R<sub>f</sub>=0.55). Fresh catalyst (10 g) was added, and the  
 reaction was placed back on the apparatus for another 4 h, at which point hydrogen uptake ceased. TLC of  
 the reaction mixture showed complete absence of starting material. The reaction mixture was filtered  
 through a pad of diatomaceous earth, and the filter cake was washed with ethanol. Evaporation of the  
 ethanol from the condensed solution left a cloudy yellow oil. This oil was dissolved in ether (1 liter), filtered  
 to remove a small amount of precipitate (dicyclohexylurea) and evaporate to give crude L-valyl-L-proline t-  
 butyl ester as a yellow oil (32.1 g, 93%).



c. [4-[(4-Chlorophenyl)sulfonylamino]benzoyl]-L-valyl-L-proline t-butyl ester.

4-Dimethylaminopyridine (16.4 g) was added to a solution of 4-[(4-chlorophenyl)sulfonylamino]benzoic acid (45.6 g) in methylene chloride (250 ml). The mixture was stirred 15 min before amine from benzene (250 ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (28.3 g), successively, were added. The reaction mixture was stirred 16 h and additional amine (1.1 g) and carbodiimide (1.5 g) were added to the reaction mixture. After an additional 3 h, the reaction was evaporated to afford a thick, grey syrup. This was dissolved in ethyl acetate, washed (20% w/w citric acid (3 times), brine (4 times)), dried (MgSO<sub>4</sub>), and evaporated. The crude material was flash chromatographed, eluting with methanol:methylene chloride (gradient: 0:1 (1.5 liter), 2:98 (1.5 liter) 4:96 (1.5 liter), 5:95 (4 liter-), to afford [4-[(4-chlorophenyl)sulfonylamino]benzoyl]-L-valyl-L-proline t-butyl ester (65.5 g, 73%) as a white foam; TLC, R<sub>f</sub> = 0.50, methanol:dichloromethane:acetic acid (2:98:1).

d. [4-[(4-Chlorophenyl)sulfonylamino]benzoyl]-L-valyl-L-proline (Formula IXa, A = CO, L = p-phenylene, R<sup>1</sup> = R<sup>2</sup>, S(O<sub>2</sub>), NH.CO-, R<sup>3</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>).

The product from Example 19c (65.5 g) was dissolved in trifluoroacetic acid (200 ml) with stirring under a nitrogen atmosphere at 0°. After one hour the reaction mixture was cooled to -15° for 16 h, after which time the reaction was poured into ice water (2 liter) with vigorous stirring. The precipitate was filtered, washed with three portions of cold water and dried under reduced pressure. The crude product was redissolved in trifluoroacetic acid (200 ml) and stirred at room temperature 18 h. The reaction mixture was poured into ice water (1.5 liter) with vigorous stirring. The precipitate was filtered and dried under high vacuum to afford the acid (59.7 g); TLC, R<sub>f</sub> = 0.05; methanol:chloroform:acetic acid (5:95:1). For further purification, the above acid (59.7 g) and calcium oxide (6.25 g) were dissolved in water (500 ml) and tetrahydrofuran (500 ml), and heated at 55-60° for 0.5 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The aqueous phase was decanted from the gummy residue and lyophilized to afford a yellow-white powder (47.3 g). This material was crystallized from methanol:water and converted back into the free acid by dissolving it in water and treating the solution with 1N HCl (pH 2) and filtering the precipitated solid.

e. N-Benzoyloxycarbonyl-L-valinal.

To a solution of the product of Example 1c (27.5 g) in acetone (1.7 liter) was added p-toluenesulfonic acid mono-hydrate (1.0 g) and the resulting solution stirred for 28 h. The solvents were evaporated; and the residue was dissolved in ether, washed (saturated NaHCO<sub>3</sub> (3 times), brine), dried (MgSO<sub>4</sub>) and evaporated to afford the aldehyde (20.6 g); TLC, R<sub>f</sub> = 0.48, methanol:chloroform (5:95); MS, m/e = 236(M+1), 192, 91.

f. (3S)-3-(Benzoyloxycarbonyl)amino-2-hydroxy-4-methylpentanenitrile (Formula XIIIa, W = CN).

A 500 ml round bottomed flask with stirrer was dried under vacuum and purged with nitrogen. The flask was charged with methylene chloride (265 ml) followed by the addition of the aldehyde product of Example 19e (20.6 g) and triethyl amine (7.40 ml). Acetone cyanohydrin (24.0 ml) was added in one portion. The reaction mixture was stirred for 6 h and the solvent evaporated. The crude product was dissolved in ether, washed (water (3 times), brine), dried (MgSO<sub>4</sub>), and evaporated. The resulting crude oil was flash chromatographed, eluting with methylene chloride:methanol:NH<sub>4</sub>OH (99:1:0.1) to afford the cyanohydrin (18.0 g, 78%) as a yellow solid; TLC, R<sub>f</sub> = 0.53, acetone:hexanes (50:50).

g. (2S)-2-[(Benzoyloxycarbonyl)amino-1-hydroxy-3-methylbutyl]benzoxazole-5-carboxamide (Formula XIVa, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl).

A 1 liter flask with stirrer was dried under vacuum and purged with nitrogen. The flask was charged with freshly distilled acetyl chloride (98.0 ml) and chloroform (100 ml) and cooled in an ice bath. Ethanol (89.0 ml) was added dropwise over 45 min maintaining the temperature below 15°. After cooling to 5°, a solution of the product of Example 19f (12.0 g) in chloroform (100 ml) was added dropwise over the course of 10 min. The reaction mixture was allowed to stir for 2 h in an ice bath and the solvent evaporated at 0° to afford a tan foam (14.1 g, 100%); TLC, after partitioning an aliquot between ethyl acetate and saturated NaHCO<sub>3</sub> to form the free imino ether, R<sub>f</sub> = 0.40, acetone:hexanes (50:50); MS, m/e = 309(M+1). m was

dissolved in absolute ethanol (230 ml) and 3-amino-4-hydroxybenzamide (7.30 g) was added. The mixture was refluxed for 1.5 h and the solvent evaporated to afford a brown solid. The solid residue was dissolved in 500 ml ethyl acetate, washed (1N HCl saturated with NaCl, saturated  $\text{NaHCO}_3/\text{NaCl}$ , brine), dried ( $\text{MgSO}_4$ ), and evaporated. This residue was dissolved in methanol, adsorbed onto diatomaceous earth, and flash chromatographed, eluting with acetone:hexanes (50:50), to afford the alcohol (7.15 g, 39%) as a tan solid; TLC,  $R_f = 0.11$ , acetone:hexanes (50:50); MS,  $m/e = 290, 246$ .

h. (2S)-(2-Amino-1-hydroxy-3-methylbutyl)benzoxazol-5-carboxamide (Formula XVa, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl).

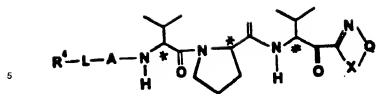
A mixture of 10% (w/w) palladium on carbon (1.26 g, 50% (w/w) water wet) and the product from Example 19g (5.00 g), in ethanol (63 ml) was hydrogenated in a shaker at 3.4 bar for 18 h. The mixture was filtered through diatomaceous earth and the solvent evaporated to afford the amine (3.13 g, 95%) as a tan solid; TLC,  $R_f = 0.20$ , methylene chloride:methanol: $\text{NH}_4\text{OH}$  (95:5:0.5); MS,  $m/e = 264$  (M+1).

i. (1S)-[4-[(4-Chlorophenyl)sulfonylamino]carbonyl]benzoyl-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]-hydroxymethyl-2-methylpropyl]-L-prolinamide (Formula III, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene,  $R^4 = R^5$ ,  $\text{S}(\text{O}_2)\text{NH}\cdot\text{CO}$ -,  $R^3 = 4\text{-ClC}_6\text{H}_4$ ).

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.57 g) was added to a solution of the product of Example 19h (1.57 g), 1-hydroxybenzotriazole (1.01 g) and the acid product of Example 19d (4.00 g) in dimethylformamide (75 ml) and the solution stirred at room temperature for 60 h. The solvent was evaporated and the brown oil washed with 1N HCl saturated with NaCl, forming a tan precipitate. After the precipitate was filtered and a portion of the solid (750 mg) was removed, the crude precipitate was dissolved in methanol, adsorbed onto diatomaceous earth and purified by flash chromatography, eluting with methylene chloride:methanol: $\text{NH}_4\text{OH}$  (gradient 85:15:1 to 70:30:1), to afford the alcohol (3.58 g, 59%) as a tan solid; TLC,  $R_f = 0.22$ , methylene chloride:methanol:acetic acid (90:10:0.2); MS,  $m/e = 421$ .

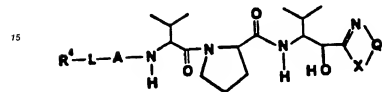
j. (S)-[4-[(4-Chlorophenyl)sulfonylamino]carbonyl]benzoyl-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide (Formula I, heterocycle containing X, N and Q = 5-(aminocarbonyl)benzoxazol-2-yl, A = CO, L = p-phenylene,  $R^4 = R^5$ ,  $\text{S}(\text{O}_2)\text{NH}\cdot\text{CO}$ -,  $R^3 = 4\text{-ClC}_6\text{H}_4$ ).

To a solution of alcohol prepared in a similar manner to that described in Example 19i, above, (50 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (183 mg) in dimethylsulfoxide (1.0 ml) and toluene (1.0 ml) was added dichloroacetic acid (8.2 mg, 0.0052 ml). The mixture was allowed to stir for 16 h, then additional dichloroacetic acid (0.011 ml) was added and stirring continued for an additional 24 h. The reaction mixture was dissolved in chloroform, washed (1N HCl, brine), dried ( $\text{MgSO}_4$ ), and the solvents evaporated to afford the title compound (42 mg).



I

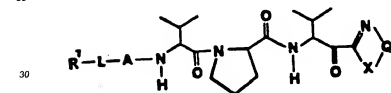
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III

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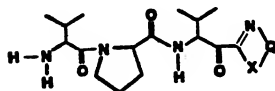


IV

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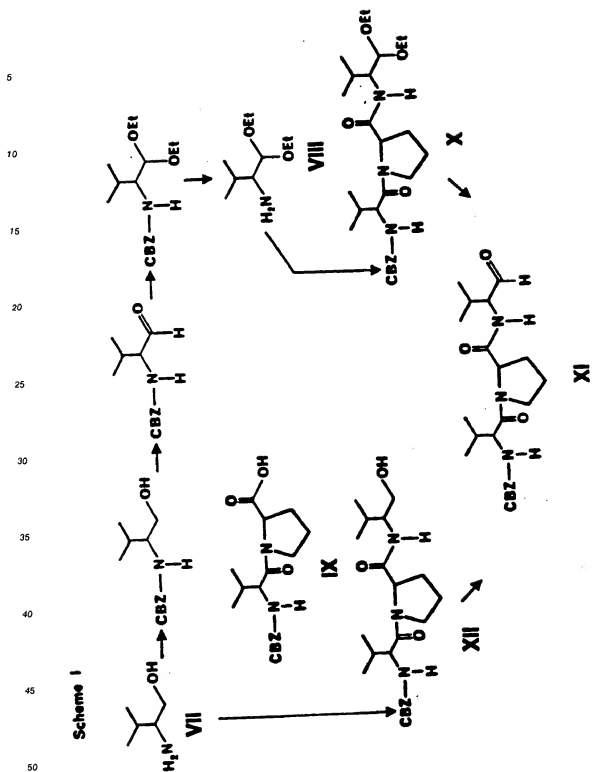
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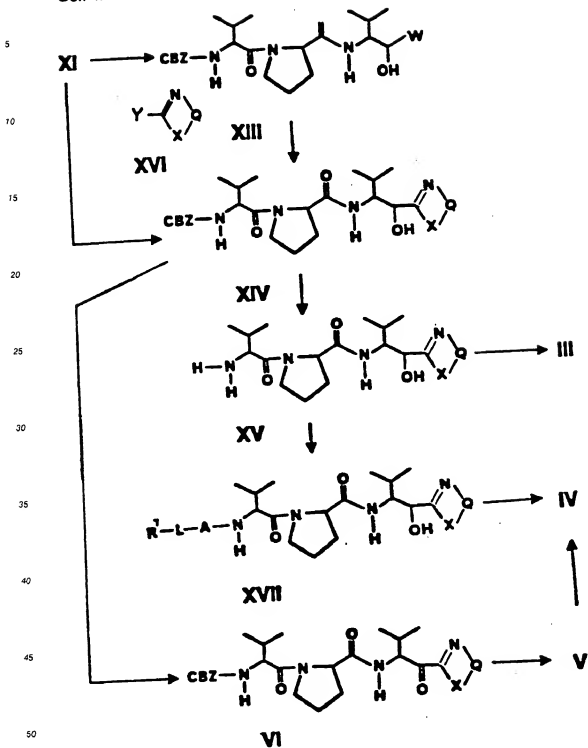
V

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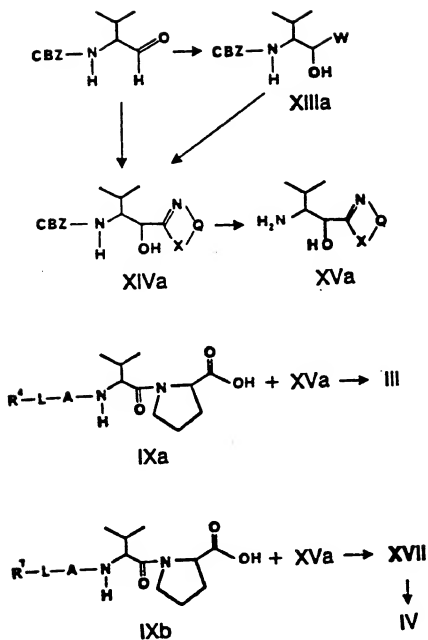
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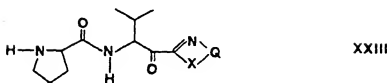
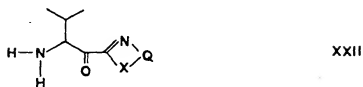
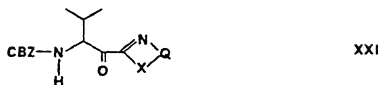
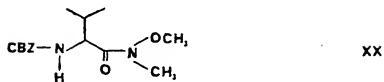
## Sch me II



## Scheme III



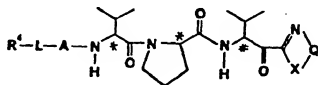
## Scheme IV



## Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

- 45 1. A compound of the following formula I,



wherein:

the group -Q- is selected from a group consisting of

- (i) ortho-phenylene, optionally bearing one or two substituents independently selected from a group consisting of halogeno, nitro, an amino group of formula -NR<sup>1</sup>R<sup>2</sup>, an acylamino group of formula

-NHCOR<sup>m</sup>, hydroxy, an acyloxy group of formula -OCOR<sup>n</sup>, (1-4C)alkoxy, (1-4C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula -CONRR<sup>p</sup> (including formula -CONRR<sup>2</sup> when R<sup>p</sup>=R<sup>q</sup>), sulfo, sulfonamido of formula SO<sub>2</sub>NR<sup>r</sup> and (1-3C)hydroxyalkyl; and

(ii) a cis-vinylene group of formula -C(R<sup>s</sup>)=C(R<sup>t</sup>)- wherein

R<sup>s</sup> and R<sup>t</sup> are each independently selected from a group consisting of hydrogen, nitro, an amino group of formula -NR<sup>u</sup>R<sup>v</sup>, an acyloxy group of formula -OCOR<sup>n</sup>, (1-6C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula -CONRR<sup>p</sup> (including formula -CONRR<sup>2</sup> when R<sup>p</sup>=R<sup>q</sup>), a hydroxymethyl group, and phenyl optionally bearing one or two substituents chosen from a group consisting of halogeno, nitro, (1-4C)alkoxy, (1-4C)alkyl and trifluoromethyl;

R<sup>u</sup>, R<sup>v</sup>, R<sup>i</sup>, R<sup>j</sup>, R<sup>m</sup>, R<sup>p</sup> and R<sup>q</sup> are each independently selected from a group consisting of hydrogen and (1-4C)alkyl;

R<sup>n</sup> is (1-4C)alkyl;

X is selected from a group consisting of oxygen and sulfur;

A is selected from a group consisting of -CO-, -NH.CO- and -O.CO-;

L is selected from a group consisting of phenylene,

(1-6C)alkenediyl, (2-6C)alkenediyl and phenylene(1-3C)alkyl optionally containing one double bond in the alkyl portion, provided that a carbon included in a double bond of an alkenediyl or included in an optional double bond of a phenylenealkyl group is not directly bonded to an oxygen or nitrogen atom of group A; and

R<sup>1</sup> is selected from a group consisting of an acylsulfonamide of formula R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, an acylsulfonamide of formula R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, a sulfonurea of formula R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, a sulfonurea of formula R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, and a trifluoromethylsulfonamide of formula CF<sub>3</sub>.S(O<sub>2</sub>).NH- wherein

R<sup>5</sup> is selected from a group consisting of (1-10C)alkyl, trifluoromethyl, (3-10C)cycloalkyl, (6 and 10C)aryl optionally substituted by 1 to 3 members of a group consisting of halogeno, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl, carboxy, phenyl, and [(1-5C)alkylcarbonyl]amino; and an aromatic heterocyclic group in which up to 3 carbons of the aromatic system may bear a substituent group independently selected from a group consisting of halogeno and trifluoromethyl; and

R<sup>6</sup> is hydrogen or methyl; and

pharmaceutically acceptable base-addition salts thereof.

2. A compound as claimed in Claim 1 wherein an optional substituent on Q when Q is ortho-phenylene is selected from a group consisting of fluoro, chloro, bromo, nitro, an amino group of formula NR<sup>u</sup>R<sup>v</sup>, an acylamino group of formula -NHCOR<sup>m</sup>, hydroxy, an acyloxy group of formula -OCOR<sup>n</sup>, methoxy, ethoxy, propoxy, isopropoxy, t-butoxy, methyl, ethyl, propyl, isopropyl, 2-methylpropyl, t-butyl, trifluoromethyl, carboxy, cyano, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, an aminocarbonyl group of formula -CONRR<sup>p</sup>, sulfo, sulfonamido of formula SO<sub>2</sub>NR<sup>r</sup>, hydroxymethyl, 2-hydroxyethyl, 1,1-dimethylhydroxymethyl, wherein R<sup>u</sup>, R<sup>v</sup>, R<sup>i</sup>, R<sup>j</sup>, R<sup>m</sup>, R<sup>p</sup> and R<sup>q</sup> are each independently selected from a group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, 2-methylpropyl and t-butyl; and R<sup>n</sup> is selected from a group consisting of hydrogen, nitro, an amino group of formula -NR<sup>u</sup>R<sup>v</sup>, an acyloxy group of formula -OCOR<sup>n</sup>, methoxy, ethoxy, propoxy, isopropoxy, t-butoxy, methyl, ethyl, propyl, isopropyl, butyl, 2-methylpropyl, t-butyl, trifluoromethyl, carboxy, cyano, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, an aminocarbonyl group of formula CONRR<sup>p</sup>, hydroxymethyl, and phenyl wherein the phenyl optionally bears one or two substituents chosen from a group consisting of fluoro, chloro, bromo, nitro, methoxy, ethoxy, propoxy, isopropoxy, t-butoxy, methyl, ethyl, propyl, isopropyl, 2-methylpropyl, t-butyl and trifluoromethyl, wherein R<sup>u</sup>, R<sup>v</sup>, R<sup>p</sup> and R<sup>q</sup> are each independently selected from a group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, 2-methylpropyl and t-butyl, and R<sup>n</sup> is selected from a group consisting of methyl, ethyl, propyl, isopropyl, 2-methylpropyl and t-butyl;

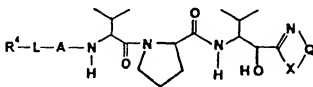
R<sup>1</sup> is selected from a group consisting of methyl, ethyl, propyl, isopropyl, t-butyl, 4-methylpentyl, trifluoromethyl, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl, phenyl, naphthyl (in which an optional substituent on the phenyl or naphthyl is fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl, carboxy, phenyl, formylamino, acetylaminio, 2-methylpropanoylamino or 2,2-dimethylpropanoylamino), furyl, thienyl, pyridyl and pyrimidinyl optionally substituted on the aromatic heterocyclic group by fluoro, chloro, bromo or trifluoromethyl; and



- L is selected from a group consisting of p-phenylene, m-phenylene, methylene, ethan-1,2-diyl, ethan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, propan-2,2-diyl, butan-1,4-diyl, 2-methylpropan-2,3-diyl, 2-methylpropan-1,2-diyl, pentan-1,5-diyl, ethen-1,2-diyl, propen-1,2-diyl, propen-1,3-diyl, buten-1,4-diyl, but-2-en-1,4-diyl, penten-1,5-diyl, 3,3-dimethylpropan-1,3-diyl, p-phenylenemethyl, 2-([p-phenylene]-ethyl), 2-([p-phenylene]-2-propyl and 2-([p-phenylene]ethenyl).
3. A compound as claimed in Claim 2 wherein an optional substituent on Q when Q is o-phenylene is chloro, dimethylamino, acetylamino, hydroxy, acetoxy, methoxy, methyl, trifluoromethyl, carboxy, cyano, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, dimethylaminosulfonyl or hydroxymethyl;
- 10  $R^a$  and  $R^b$  are each independently selected from a group consisting of hydrogen, dimethylamino, acetoxy, methoxy, methyl, trifluoromethyl, cyano, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, hydroxymethyl, phenyl, chlorophenyl, methoxyphenyl and trifluoromethylphenyl;
- 15  $R^c$  is  $R^d.S(O_2).NH.CO-$ ,  
 $R^d.S(O_2).NH.CO.NR^e-$ , or  $CF_3SO_2NH-$ ;  $R^e$  is selected from a group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclopentyl, phenyl, chlorophenyl, bromophenyl, trifluoromethylphenyl, 1-naphthyl, 2-thienyl, 2-pyridyl and chloropyridyl;
- 20  $R^f$  is hydrogen;  
 A is -CO-; and  
 L is p-phenylene, ethane-1,2-diyl, ethen-1,2-diyl, p-phenylenemethyl or 2-([p-phenylene]ethenyl).
4. A compound as claimed in Claim 3 wherein an optional substituent on Q is hydroxy, methoxy, carboxy, methoxycarbonyl, aminocarbonyl or hydroxymethyl;
- 25  $R^a$  and  $R^b$  are hydrogen;  
 $R^c$  is methyl, isopropyl, phenyl or 4-chloro-phenyl; and  
 L is p-phenylene.
5. A compound as claimed in Claim 1 selected from a group consisting of a benzoxazole wherein X is oxygen and Q is ortho-phenylene, an oxazole wherein X is oxygen and Q is a cis-vinylene group of formula  $-C(R^a)=C(R^b)-$ , a benzothiazole wherein X is sulfur and Q is ortho-phenylene, and a thiazole wherein X is sulfur and Q is a cis-vinylene group of formula  $-C(R^a)=C(R^b)-$  and wherein an ortho-phenylene group may optionally bear one or two substituents independently selected from a group consisting of halogeno, nitro, an amino group of formula  $-NR^aR^b$ , hydroxy, acetoxy, (1-4C)alkoxy, (1-4C)alkyl, trifluoromethyl, carboxy, [(1-4C)alkoxy]carbonyl, sulfo and a sulfonamido of formula  $SO_2NR^aR^b$ ; and
- 30 wherein  
 $R^a$  and  $R^b$  are each independently selected from a group consisting of hydrogen, nitro, an amino group of formula  $-NR^aR^b$ , (1-4C)alkoxy, (1-6C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, and phenyl optionally bearing one or two substituents chosen from a group consisting of halogeno, nitro, (1-4C)alkoxy, (1-4C)alkyl and trifluoromethyl;
- 35  $R^c$ ,  $R^d$ ,  $R^e$  and  $R^f$  are each independently selected from a group consisting of hydrogen and (1-4C)-alkyl;  
 A is selected from a group consisting of -CO-, -NH.CO- and -O.CO-;
- 45 L is selected from a group consisting of phenylene, (1-6C)alkanediyl, (2-6C)alkenediyl and phenylene(1-3C)alkyl, optionally containing one double bond in the alkyl portion, provided that a double bond of an alkenediyl or an optional double bond of a phenylenealkyl group is not directly bonded to an oxygen or nitrogen atom of group A; and  
 $R^d$  is selected from a group consisting of acylsulfonamide of formula  $R^f.S(O_2).NH.CO-$ , acylsulfonamide of formula  $R^f.CO.NH.S(O_2)-$ , sulfonyleurea of formula  $R^f.NH.CO.NH.S(O_2)-$  and sulfonyleurea of formula  $R^f.S(O_2).NH.CO.NR^e-$  wherein
- 50  $R^f$  is selected from a group consisting of (1-10C)alkyl, trifluoromethyl, (3-10C)cycloalkyl, (6 and 10C)aryl optionally substituted by 1 to 3 members selected from a group consisting of halogeno, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl, carboxy, phenyl, and [(1-5C)alkylcarbonyl]amino; and an aromatic heterocyclic group in which up to 3 carbons of the aromatic heterocyclic group may bear a substituent group independently selected from a group consisting of halogeno and trifluoromethyl; and  
 $R^e$  is hydrogen or methyl; and
- 55

pharmaceutically acceptable base-addition salts thereof.

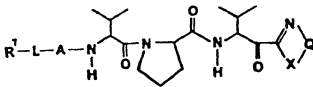
6. A compound as claimed in Claim 1 selected from a group consisting of:
- (a) a benzoxazole wherein X is oxygen and Q is *o*-phenylene as defined under (i) in the definition of Q;
  - (b) an oxazole wherein X is oxygen and Q is *cis*-vinylene as defined under (ii) in the definition of Q;
  - (c) a benzothiazole wherein X is sulfur and Q is *o*-phenylene as defined under (i) in the definition of Q; and
  - (d) a thiazole wherein X is sulfur and Q is *cis*-vinylene as defined under (ii) in the definition of Q.
- and pharmaceutically acceptable base-addition salts thereof.
7. A compound as claimed in any one of Claims 1, 2, 3, 5 or 6 wherein X is oxygen; R<sup>4</sup> is R<sup>5</sup>.S(O<sub>2</sub>).NH.CO- or R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-; L is *p*-phenylene; A is -CO-; and R<sup>5</sup> is 4-chlorophenyl.
8. A compound as claimed in Claim 4 wherein X is oxygen; R<sup>4</sup> is R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-; L is *p*-phenylene; A is -CO-; and R<sup>5</sup> is 4-chlorophenyl.
9. A compound as claimed in Claim 1 selected from a group consisting of:
- (i) [4-[(4-chlorophenyl)sulfonylamino]carbonyl]benzoyl-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)carbonyl-2-methylpropyl]-L-prolinamide;
  - (ii) [4-[(4-chlorophenyl)sulfonylamino]carbonyl]benzoyl-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide; and
  - (iii) [4-[(4-chlorophenyl)sulfonylamino]carbonyl]benzoyl-L-valyl-N-[1-[5-hydroxymethyl]benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamide;
- and pharmaceutically acceptable base-addition salts thereof.
10. A salt as claimed in Claim 1 wherein said salt is made with a base forming a physiologically acceptable cation.
11. A compound of the following formula III,



III

wherein R<sup>4</sup>, L, A, Q and X are defined as in Claim 1, or a salt thereof.

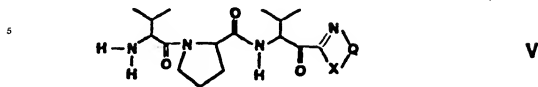
12. A compound of the following formula IV,



IV

wherein R<sup>7</sup> is selected from a group consisting of carboxy, H<sub>2</sub>N.S(O<sub>2</sub>)-, HNR<sup>6</sup>- and -NCO, and wherein R<sup>6</sup>, L, A, Q and X are defined as in Claim 1, or a salt thereof.

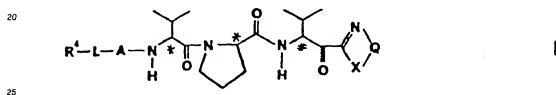
13. A compound of the following formula V,



10 wherein Q and X are defined as in Claim 1, or a salt thereof.

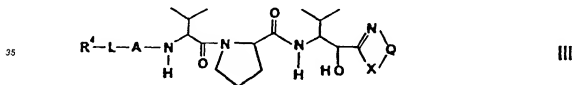
14. A pharmaceutical composition comprising a leukocyte elastase inhibiting amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

15. A method of making a compound of the following formula I,

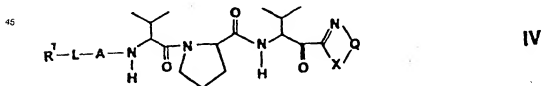


25 or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1-10 which is characterized by:

(A) for a compound of formula I, oxidizing a corresponding alcohol of formula III,



40 (B) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, reacting a corresponding compound of the following formula IV,



50 wherein R<sup>1</sup> is carboxy (which compound is hereinafter referred to as "acid of formula IV") with a sulfonamide derivative of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> in the presence of a dehydrating agent or reacting a reactive derivative of an acid of formula IV with a sulfonamide, or a salt thereof, of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub>;

55 (B-1) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, reacting a reactive derivative of an acid of said formula IV with an alkali metal salt of a selected sulfonamide of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> in a suitable solvent or diluent;

(C) for a compound of formula I wherein  $R^4$  has the value  $R^5.CO.NH.S(O_2)-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $H_2N.S(O_2)-$  with an acid of formula  $R^5.CO.OH$ ;

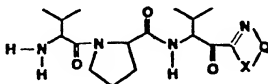
(D) for a compound of formula I wherein  $R^4$  has the value  $R^5.NH.CO.NH.S(O_2)-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $H_2N.S(O_2)-$  with an isocyanate of formula  $R^5.NCO$ ;

(E) for a compound of formula I wherein  $R^4$  has the value  $R^5.S(O_2).NH.CO.NR^6-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $HNR^6-$  with a sulfonylisocyanate of formula  $R^5.S(O_2).NCO$ ;

(E-1) for a compound of formula I wherein  $R^4$  has the value  $R^5.S(O_2).NH.CO.NR^6-$ , wherein  $R^6$  is hydrogen, reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $-NCO$  with a sulfonamide of formula  $R^5.S(O_2).NH_2$ ;

(F) for a compound of formula I wherein  $R^4$  has the value  $CF_3.S(O_2).NH-$ , reacting a corresponding amine of said formula IV in which  $R^7$  has the value  $H_2N-$  with trifluoromethanesulfonic anhydride;

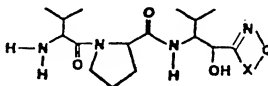
(G) for a compound of formula I wherein A has the value  $-CO-$ , coupling an acid of formula  $R^4-L-COOH$  (or a reactive derivative thereof) with an amino ketone of the following V,



V

whereafter, when a pharmaceutically acceptable salt is required, reacting an acidic form of the compound of formula I with a base to afford a physiologically acceptable cation.

16. A compound of the formula XV,

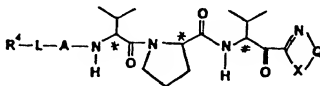


XV

wherein Q and X are as defined in claim 1, or a salt thereof.

Claims for the following Contracting State : ES

1. A process for preparing a compound of the following formula I,



I

wherein:

(i) the group  $-Q-$  is selected from a group consisting of (i) ortho-phenylene, optionally bearing one or two substituents independently selected from a group consisting of halogeno, nitro, an amino group of formula  $-NR^2R^3$ , an acylamino group of formula  $-NHCOR^4$ , hydroxy, an acyloxy group of formula  $-OCOR^4$ , (1-4C)alkoxy, (1-4C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-CONR^2R^3$  (including

formula  $-\text{CONR}^2$  when  $\text{R}^2 = \text{R}^3$ ), sulfo, sulfonamido of formula  $\text{SO}_2\text{NR}^3$  and (1-3C)hydroxyalkyl; and

(ii) a cis-vinylene group of formula  $-\text{C}(\text{R}^a)=\text{C}(\text{R}^b)-$  wherein

$\text{R}^a$  and  $\text{R}^b$  are each independently selected from a group consisting of hydrogen, nitro, an amino group of formula  $-\text{NR}^2\text{R}^3$ , an acyloxy group of formula  $-\text{OCOR}^4$ , (1-4C)alkoxy, (1-6C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-\text{CONR}^2\text{R}^3-$  (including formula  $-\text{CONR}^2$  when  $\text{R}^2 = \text{R}^3$ ), a hydroxymethyl group, and phenyl optionally bearing one or two substituents chosen from a group consisting of halogeno, nitro, (1-4C)alkoxy, (1-4C)alkyl and trifluoromethyl;

$\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are each independently selected from a group consisting of hydrogen and (1-4C)alkyl;

$\text{R}^8$  is (1-4C)alkyl;

X is selected from a group consisting of oxygen and sulfur;

A is selected from a group consisting of  $-\text{CO}-$ ,  $-\text{NH.CO}-$  and  $-\text{O.CO}-$ ;

L is selected from a group consisting of phenylene, (1-6C)alkanediyl, (2-6C)alkenediyl and phenylene(1-3C)alkyl optionally containing one double bond in the alkyl portion, provided that a carbon included in a double bond of an alkenediyl or included in an optional double bond of a phenylenealkyl group is not directly bonded to an oxygen or nitrogen atom of group A; and

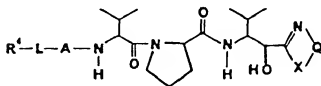
$\text{R}^4$  is selected from a group consisting of an acylsulfonamide of formula  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$ , an acylsulfonamide of formula  $\text{R}^5.\text{CO.NH.S}(\text{O}_2)-$ , a sulfonylurea of formula  $\text{R}^5.\text{NH.CO.NH.S}(\text{O}_2)-$ , a sulfonylurea of formula  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO.NR}^6-$ , and a trifluoromethylsulfonamide of formula  $\text{CF}_3.\text{S}(\text{O}_2).\text{NH}-$  wherein

$\text{R}^5$  is selected from a group consisting of (1-10C)alkyl, trifluoromethyl, (3-10C)cycloalkyl, (6 and 10C)aryl optionally substituted by 1 to 3 members of a group consisting of halogeno, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl, carboxy, phenyl, and [(1-5C)alkylcarbonyl]amino; and an aromatic heterocyclic group in which up to 3 carbons of the aromatic system may bear a substituent group independently selected from a group consisting of halogeno and trifluoromethyl; and

$\text{R}^6$  is hydrogen or methyl;

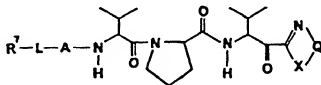
wherein said process comprises a process selected from a group consisting of

(A) for a compound of formula I, oxidizing a corresponding alcohol of formula III,



III

(B) for a compound of formula I wherein  $\text{R}^4$  has the value  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$ , reacting a corresponding compound of the following formula IV,



IV

wherein  $\text{R}^7$  is carboxy (which compound is hereinafter referred to as "acid of formula IV") with a sulfonamide derivative of formula  $\text{R}^5.\text{S}(\text{O}_2).\text{NH}_2$  in the presence of a dehydrating agent or reacting a reactive derivative of an acid of formula IV with a sulfonamide, or a salt thereof, of formula  $\text{R}^5.\text{S}(\text{O}_2).\text{NH}_2$ ;

(B-1) for a compound of formula I wherein  $\text{R}^4$  has the value  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$ , reacting a reactive derivative of an acid of said formula IV with an alkali metal salt of a selected sulfonamide of formula  $\text{R}^5.\text{S}(\text{O}_2).\text{NH}_2$  in a suitable solvent or diluent;

(C) for a compound of formula I wherein  $R^4$  has the value  $R^6.CO.NH.S(O_2)_-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $H_2N.S(O_2)_-$  with an acid of formula  $R^5.CO.OH$ ;

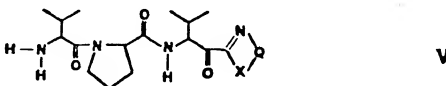
(D) for a compound of formula I wherein  $R^4$  has the value  $R^5.NH.CO.NH.S(O_2)_-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $H_2N.S(O_2)_-$  with an isocyanate of formula  $R^5.NCO$ ;

(E) for a compound of formula I wherein  $R^4$  has the value  $R^5.S(O_2).NH.CO.NR^6-$ , reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $HNR^6-$  with a sulfonylisocyanate of formula  $R^5.S(O_2).NCO$ ;

(E-1) for a compound of formula I wherein  $R^4$  has the value  $R^5.S(O_2).NH.CO.NR^6-$ , wherein  $R^6$  is hydrogen, reacting a corresponding compound of said formula IV in which  $R^7$  has the value  $-NCO$  with a sulfonamide of formula  $R^5.S(O_2).NH_2$ ;

(F) for a compound of formula I wherein  $R^4$  has the value  $CF_3.S(O_2).NH-$ , reacting a corresponding amine of said formula IV in which  $R^7$  has the value  $H_2N-$  with trifluoromethanesulfonic anhydride;

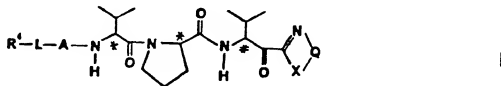
(G) for a compound of formula I wherein A has the value  $-CO-$ , coupling an acid of formula  $R^4-L-COOH$  (or a reactive derivative thereof) with an amino ketone of the following V,



and whereafter, when a pharmaceutically acceptable salt is required, reacting an acidic form of the compound of formula I with a base to afford a physiologically acceptable cation.

#### Claims for the following Contracting State : GR

1. A process for preparing a compound of the following formula I,



wherein:

the group -O- is selected from a group consisting of

- (i) *ortho*-phenylene, optionally bearing one or two substituents independently selected from a group consisting of halogeno, nitro, an amino group of formula  $-NR^aR^b$ , an acylamino group of formula  $-NHCOR^m$ , hydroxy, an acyloxy group of formula  $-OCOR^a$ , (1-4C)alkoxy, (1-4C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-CONR^aR^b$  (including formula  $-CONR^2$  when  $R^b=R^a$ ), sulfo, sulfonamido of formula  $SO_2NR^1R^2$  and (1-3C)hydroxyalkyl; and

- (ii) a *cis*-vinylene group of formula  $-C(R^*)=C(R^*)-$  wherein

$R^a$  and  $R^b$  are each independently selected from a group consisting of hydrogen, nitro, an amino group of formula  $-NR^aR^b$ , an acyloxy group of formula  $OCOR^a$ , (1-4C)alkoxy, (1-6C)alkyl, trifluoromethyl, carboxy, cyano, [(1-4C)alkoxy]carbonyl, an aminocarbonyl group of formula  $-CONR^aR^b-$  (including formula  $-CONR^2$  when  $R^b=R^a$ ), a hydroxymethyl group, and phenyl optionally bearing one or two substituents chosen from a group consisting of halogeno, nitro, (1-4C)alkoxy, (1-4C)alkyl and trifluoromethyl;

$R^a$ ,  $R^b$ ,  $R^1$ ,  $R^2$ ,  $R^m$ ,  $R^p$  and  $R^q$  are each independently selected from a group consisting of hydrogen and (1-4C)alkyl;

R<sup>n</sup> is (1-4C)alkyl;

X is selected from a group consisting of oxygen and sulfur;

A is selected from a group consisting of -CO-, -NH.CO- and -O.CO-;

L is selected from a group consisting of phenylene, (1-6C)alkanediy, (2-6C)alkenediy and phenylene(1-3C)alkyl optionally containing one double bond in the alkyl portion, provided that a carbon included in a double bond of an alkenediy or included in an optional double bond of a phenylenealkyl group is not directly bonded to an oxygen or nitrogen atom of group A; and

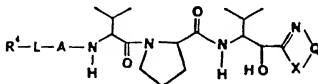
R<sup>4</sup> is selected from a group consisting of an acylsulfonamide of formula R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, an acylsulfonamide of formula R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, a sulfonyleurea of formula R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, a sulfonyleurea of formula R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, and a trifluoromethylsulfonamide of formula CF<sub>3</sub>.S(O<sub>2</sub>).NH- wherein

R<sup>5</sup> is selected from a group consisting of (1-10C)alkyl, trifluoromethyl, (3-10C)cycloalkyl, (6 and 10C)aryl optionally substituted by 1 to 3 members of a group consisting of halogeno, nitro, amino, dimethylamino, hydroxy, methyl, trifluoromethyl, carboxy, phenyl, and [(1-5C)alkylcarbonyl]amino; and an aromatic heterocyclic group in which up to 3 carbons of the aromatic system may bear a substituent group independently selected from a group consisting of halogeno and trifluoromethyl; and

R<sup>6</sup> is hydrogen or methyl;

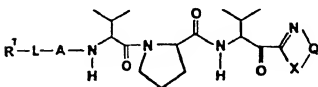
wherein said process comprises a process selected from a group consisting of

(A) for a compound of formula I, oxidizing a corresponding alcohol of formula III,



III

(B) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, reacting a corresponding compound of the following formula IV,



IV

wherein R<sup>7</sup> is carboxy (which compound is hereinafter referred to as "acid of formula IV") with a sulfonamide derivative of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> in the presence of a dehydrating agent or reacting a reactive derivative of an acid of formula IV with a sulfonamide, or a salt thereof, of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub>;

(B-1) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, reacting a reactive derivative of an acid of said formula IV with an alkali metal salt of a selected sulfonamide of formula R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> in a suitable solvent or diluent;

(C) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, reacting a corresponding compound of said formula IV in which R<sup>7</sup> has the value H<sub>2</sub>N.S(O<sub>2</sub>)- with an acid of formula R<sup>5</sup>.COOH;

(D) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, reacting a corresponding compound of said formula IV in which R<sup>7</sup> has the value H<sub>2</sub>N.S(O<sub>2</sub>)- with an isocyanate of formula R<sup>5</sup>.NCO;

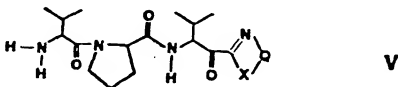
(E) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, reacting a corresponding compound of said formula IV in which R<sup>7</sup> has the value HNR<sup>6</sup>- with a sulfonyleisocyanate of formula R<sup>5</sup>.S(O<sub>2</sub>).NCO;

(E-1) for a compound of formula I wherein R<sup>4</sup> has the value R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, wherein R<sup>6</sup> is hydrogen, reacting a corresponding compound of said formula IV in which R<sup>7</sup> has the value -NCO

with a sulfonamide of formula  $R^5 \cdot S(O_2) \cdot NH_2$ ;

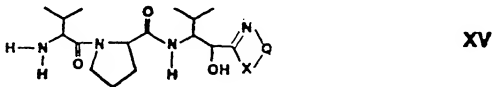
(F) for a compound of formula I wherein  $R^4$  has the value  $CF_3 \cdot S(O_2) \cdot NH-$ , reacting a corresponding amine of said formula IV in which  $R^7$  has the value  $H_2N-$  with trifluoromethanesulfonic anhydride;

(G) for a compound of formula I wherein A has the value  $-CO-$ , coupling an acid of formula  $R^4-L-COOH$  (or a reactive derivative thereof) with an amino ketone of the following V,



and whereafter, when a pharmaceutically acceptable salt is required, reacting an acidic form of the compound of formula I with a base to afford a physiologically acceptable cation.

2. A compound of formula III as set out in Claim 1 wherein  $R^4$ , L, A, Q and X are defined as in Claim 1, or a salt thereof.
3. A compound of formula IV as set out in Claim 1 wherein  $R^7$  is selected from a group consisting of carboxy,  $H_2N \cdot S(O_2)-$ ,  $HNR^5-$  and  $-NCO$ , and wherein  $R^4$ , L, A, Q and X are defined as in Claim 1, or a salt thereof.
4. A compound of formula V as set out in Claim 1 wherein Q and X are defined as in Claim 1, or a salt thereof.
5. A compound of the formula XV,

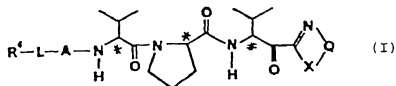


wherein Q and X are as defined in claim 1, or a salt thereof.

#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindungen der Formel I



worin:

Q ausgewählt ist aus

(i) ortho-Phenylene, das gegebenenfalls einen oder zwei Substituenten trägt, die unabhängig ausgewählt sind aus Halogeno, Nitro, Amino-Gruppen der Formel  $-NR^6R^8$ , Acylamino-Gruppen der Formel

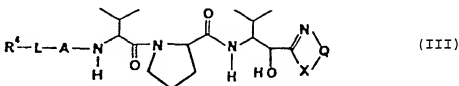


- NHCOR<sup>m</sup>, Hydroxy, Acyloxy-Gruppen der Formel -OCOR<sup>n</sup>, (1-4C)Alkoxy, (1-4C)Alkyl, Trifluoromethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl, Aminocarbonyl-Gruppen der Formel -CONR<sup>p</sup>R<sup>q</sup> - (einschließlich der Formel -CONR<sup>p</sup><sub>2</sub>, wenn R<sup>p</sup>=R<sup>q</sup>), Sulfo, Sulfonamido-Gruppen der Formel -SO<sub>2</sub>NR<sup>r</sup>R<sup>s</sup> und (1-3C)Hydroxyalkyl; und
- (ii) cis-Vinylen-Gruppen der Formel -C(R<sup>a</sup>)=C(R<sup>b</sup>)<sub>2</sub>;
- R<sup>a</sup> und R<sup>b</sup> unabhängig ausgewählt sind aus Wasserstoff, Nitro, Amino-Gruppen der Formel -NR<sup>r</sup>R<sup>s</sup>, Acyloxy-Gruppen der Formel -OCOR<sup>n</sup>, (1-4C)Alkoxy, (1-6C)Alkyl, Trifluoromethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl, Aminocarbonyl-Gruppen der Formel -CONR<sup>p</sup>R<sup>q</sup> (einschließlich der Formel -CONR<sup>p</sup><sub>2</sub>, wenn R<sup>p</sup>=R<sup>q</sup>), Hydroxymethyl und Phenyl, das gegebenenfalls einen oder zwei Substituenten trägt, die ausgewählt sind aus Halogeno, Nitro, (1-4C)Alkoxy, (1-4C)Alkyl und Trifluoromethyl;
- R<sup>r</sup>, R<sup>s</sup>, R<sup>t</sup>, R<sup>l</sup>, R<sup>m</sup>, R<sup>n</sup> und R<sup>q</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff und (1-4C)Alkyl; R<sup>n</sup> für (1-4C)Alkyl steht;
- X ausgewählt ist aus Sauerstoff und Schwefel;
- A ausgewählt ist aus -CO-, -NH.CO- und -O.CO-;
- L ausgewählt ist aus Phenylen, (1-6C)Alkandyl, (2-6C)Alkendiyl und Phenylen(1-3C)alkyl, das gegebenenfalls im Alkyl-Teil eine Doppelbindung enthält, mit der Maßgabe, daß ein Kohlenstoffatom, das an einer Doppelbindung eines Alkendiols oder einer fakultativen Doppelbindung eines Phenylalkyls beteiligt ist, nicht direkt an ein Sauerstoff- oder Stickstoffatom der Gruppe A gebunden ist;
- R<sup>4</sup> ausgewählt ist aus Acylsulfonamid-Gruppen der Formel R<sup>3</sup>.S(O<sub>2</sub>).NH.CO-, Acylsulfonamid-Gruppen der Formel R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, Sulfonylharnstoff-Gruppen der Formel R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>- und Trifluoromethylsulfonamid (CF<sub>3</sub>.S(O<sub>2</sub>).NH-);
- R<sup>5</sup> ausgewählt ist aus (1-10C)Alkyl, Trifluoromethyl, (3-10C)Cycloalkyl, (6 und 10C)Aryl, das gegebenenfalls 1 bis 3 Halogeno-, Nitro-, Amino-, Dimethylamino-, Hydroxy-, Methyl-, Trifluoromethyl-, Carboxy-, Phenyl- oder [(1-5C)Alkylcarbonyl]amino-Substituenten trägt, und aromatischen heterocyclischen Gruppen, in denen bis zu 3 Kohlenstoffatome des aromatischen Systems gegebenenfalls unabhängig einen Halogeno- oder Trifluoromethyl-Substituenten tragen; und
- R<sup>6</sup> für Wasserstoff oder Methyl steht;
- sowie die pharmazeutisch zulässigen Basenadditionssalze davon.
2. Verbindungen nach Anspruch 1, bei denen ein fakultativer Substituent an Q, sofern Q für ortho-Phenylen steht, ausgewählt ist Fluoro, Chloro, Bromo, Nitro, Amino-Gruppen der Formel -NR<sup>r</sup>R<sup>s</sup>, Acylamino-Gruppen der Formel -NHCOR<sup>m</sup>, Hydroxy, Acyloxy-Gruppen der Formel -OCOR<sup>n</sup>, Methoxy, Ethoxy, Propoxy, Isopropoxy, t-Butoxy, Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl, t-Butyl, Trifluoromethyl, Carboxy, Cyano, Methoxycarbonyl, Ethoxycarbonyl, t-Butoxycarbonyl, Aminocarbonyl-Gruppen der Formel -CONR<sup>p</sup>R<sup>q</sup>, Sulfo, Sulfonamido-Gruppen der Formel SO<sub>2</sub>NR<sup>r</sup>R<sup>s</sup>, Hydroxymethyl, 2-Hydroxyethyl und 1,1-Dimethylhydroxymethyl;
- R<sup>r</sup>, R<sup>s</sup>, R<sup>t</sup>, R<sup>l</sup>, R<sup>m</sup>, R<sup>n</sup> und R<sup>q</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl und t-Butyl;
- R<sup>4</sup> ausgewählt ist aus Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl und t-Butyl;
- R<sup>8</sup> und R<sup>9</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff, Nitro, Amino-Gruppen der Formel -NR<sup>r</sup>R<sup>s</sup>, Acyloxy-Gruppen der Formel -OCOR<sup>n</sup>, Methoxy, Ethoxy, Propoxy, Isopropoxy, t-Butoxy, Methyl, Ethyl, Propyl, Isopropyl, Butyl, 2-Methylpropyl, t-Butyl, Trifluoromethyl, Carboxy, Cyano, Methoxycarbonyl, Ethoxycarbonyl, t-Butoxycarbonyl, Aminocarbonyl-Gruppen der Formel -CONR<sup>p</sup>R<sup>q</sup>, Hydroxymethyl und Phenyl, wobei das Phenyl gegebenenfalls einen oder zwei Substituenten trägt, die ausgewählt sind Fluoro, Chloro, Bromo, Nitro, Methoxy, Ethoxy, Propoxy, Isopropoxy, t-Butoxy, Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl, t-Butyl und Trifluoromethyl;
- R<sup>8</sup>, R<sup>9</sup>, R<sup>0</sup> und R<sup>4</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff, Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl und t-Butyl;
- R<sup>5</sup> ausgewählt ist aus Methyl, Ethyl, Propyl, Isopropyl, 2-Methylpropyl und t-Butyl;
- R<sup>3</sup> ausgewählt ist aus Methyl, Ethyl, Propyl, Isopropyl, t-Butyl, 4-Methylpentyl, Trifluoromethyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, Norbornyl, Adamantyl, Phenyl, Naphthyl (wobei ein fakultativer Substituent am Phenyl oder Naphthyl aus Fluoro, Chloro, Bromo, Nitro, Amino, Dimethylamino, Hydroxy, Methyl, Trifluoromethyl, Carboxy, Phenyl, Formylamino, Acetylamino, 2-Methylpropanoylamino oder 2,2-Dimethylpropanoylamino besteht), Furyl, Thienyl, Pyridyl und Pyrimidinyl, das gegebenenfalls an der aromatischen heterocyclischen Gruppe durch Fluoro, Chloro, Bromo oder Trifluoromethyl substituiert ist; und
- L ausgewählt ist aus p-Phenylen, m-Phenylen, Methylene, Ethan-1,2-diyl, Ethan-1,1-diyl, Propan-1,3-diyl, Propan-1,2-diyl, Propan-2,2-diyl, Butan-1,4-diyl, 2-Methylpropan-2,3-diyl, 2-Methylpropan-1,2-diyl, Pen-

tan-1,5-diyl, Ethen-1,2-diyl, Propen-1,2-diyl, Propen-1,3-diyl, Buten-1,4-diyl, But-2-en-1,4-diyl, Penten-1,5-diyl, 3,3-Dimethylpropen-1,3-diyl, p-Phenylenmethyl, 2-(p-Phenylen)ethyl, 2-(p-Phenylen)-2-propyl und 2-(p-Phenylen)ethenyl.

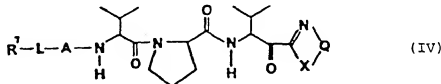
3. Verbindung nach Anspruch 2, bei denen ein fakultativer Substituent an Q, sofern Q für o-Phenylen steht, ausgewählt ist aus Chloro, Dimethylamino, Acetylamino, Hydroxy, Acetoxy, Methoxy, Methyl, Trifluoromethyl, Carboxy, Cyano, Methoxycarbonyl, Ethoxycarbonyl, Aminocarbonyl, Methylaminocarbonyl, Dimethylaminocarbonyl, Aminosulfonyl, Dimethylaminosulfonyl und Hydroxymethyl;  
R<sup>a</sup> und R<sup>b</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff, Dimethylamino, Acetoxy, Methoxy, Methyl, Trifluoromethyl, Cyano, Methoxycarbonyl, Aminocarbonyl, Methylaminocarbonyl, Dimethylaminocarbonyl, Hydroxymethyl, Phenyl, Chlorophenyl, Methoxyphenyl und Trifluoromethylphenyl;  
R<sup>c</sup> für R<sup>d</sup>.S(O<sub>2</sub>).NH.CO-, R<sup>d</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>e</sup>- oder CF<sub>3</sub>SO<sub>2</sub>NH- steht;  
R<sup>e</sup> ausgewählt ist aus Methyl, Ethyl, Isopropyl, Cyclopropyl, Cyclopentyl, Phenyl, Chlorophenyl, Bromophenyl, Trifluoromethylphenyl, 1-Naphthyl, 2-Thienyl, 2-Pyridyl und Chloropyridyl;  
R<sup>f</sup> für Wasserstoff steht;  
A für -CO- steht;  
L für p-Phenylen, Ethen-1,2-diyl, Ethen-1,2-diyl, p-Phenylenmethyl oder 2-(p-Phenylen)ethenyl steht.
4. Verbindung nach Anspruch 3, bei denen ein fakultativer Substituent an Q ausgewählt ist aus Hydroxy, Methoxy, Carboxy, Methoxycarbonyl, Aminocarbonyl und Hydroxymethyl;  
R<sup>a</sup> und R<sup>b</sup> für Wasserstoff stehen;  
R<sup>c</sup> für Methyl, Isopropyl, Phenyl oder 4-Chloro-phenyl steht; und  
L für p-Phenylen steht.
5. Verbindungen nach Anspruch 1, welche ausgewählt sind aus einem Benzoxazol, worin X für Sauerstoff steht und Q für ortho-Phenylen steht, einem Oxazol, worin X für Sauerstoff steht und Q für eine cis-Vinylen-Gruppe der Formel -C(R<sup>a</sup>)=C(R<sup>b</sup>)- steht, einem Benzothiazol, worin X für Schwefel steht und Q für ortho-Phenylen steht, und einem Thiazol, worin X für Schwefel steht und Q für eine cis-Vinylen-Gruppe der Formel -C(R<sup>a</sup>)=C(R<sup>b</sup>)-steht, wobei eine ortho-Phenylen-Gruppe gegebenenfalls einen oder zwei Substituenten trägt, die unabhängig ausgewählt sind Halogeno, Nitro, Amino-Gruppen der Formel -NR<sup>a</sup>R<sup>b</sup>, Hydroxy, Acetoxy, (1-4C)Alkoxy, (1-4C)alkyl, Trifluoromethyl, Carboxy, [(1-4C)Alkoxy]carbonyl, Sulfo und Sulfonamido-Gruppen der Formel -SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>;  
R<sup>a</sup> und R<sup>b</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff, Nitro, Amino-Gruppen der Formel -NR<sup>a</sup>R<sup>b</sup>, (1-4C)Alkoxy, (1-6C)Alkyl, Trifluoromethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl und Phenyl, das gegebenenfalls einen oder zwei Substituenten trägt, die ausgewählt sind aus Halogeno, Nitro, (1-4C)Alkoxy, (1-4C)Alkyl und Trifluoromethyl;  
R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup> und R<sup>d</sup> jeweils unabhängig ausgewählt sind aus Wasserstoff und (1-4C)Alkyl;  
A ausgewählt ist aus -CO-, -NH.CO- und -O.CO-;  
L ausgewählt ist aus Phenylen, (1-6C)Alkandiyl, (2-6C)Alkendiyl und Phenylen(1-3C)alkyl, das gegebenenfalls im Alkyl-Teil eine Doppelbindung enthält, mit der Maßgabe, daß eine Doppelbindung eines Alkendiyls oder eine fakultative Doppelbindung eines Phenylenalkyls nicht direkt an ein Sauerstoff- oder Stickstoffatom der Gruppe A gebunden ist;  
R<sup>e</sup> ausgewählt ist aus Acylsulfonamid-Gruppen der Formel R<sup>f</sup>.S(O<sub>2</sub>).NH.CO-, Acylsulfonamid-Gruppen der Formel R<sup>f</sup>.CO.NH.S(O<sub>2</sub>)-, Sulfonylharnstoff-Gruppen der Formel R<sup>f</sup>.NH.CO.NH.S(O<sub>2</sub>)- und Sulfonylharnstoff-Gruppen der Formel R<sup>f</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>g</sup>-;  
R<sup>f</sup> ausgewählt ist aus (1-10C)Alkyl, Trifluoromethyl, (3-10C)Cycloalkyl, (6 und 10C)Aryl, das gegebenenfalls 1 bis 3 Halogeno-, Nitro-, Amino-, Dimethylamino-, Hydroxy-, Methyl-, Trifluoromethyl-, Carboxy-, Phenyl- oder [(1-5C)Alkylcarbonyl]amino-Substituenten trägt, und aromatischen heterocyclischen Gruppen, in denen bis zu 3 Kohlenstoffatome der aromatischen heterocyclischen Gruppe gegebenenfalls einen Substituenten tragen, der jeweils unabhängig ausgewählt ist aus Halogeno und Trifluoromethyl; und  
R<sup>g</sup> für Wasserstoff oder Methyl steht;  
sowie die pharmazeutisch zulässigen Basen-Additionssalze davon.
6. Verbindungen nach Anspruch 1, welche ausgewählt sind aus:  
(a) einem Benzoxazol, worin X für Sauerstoff steht und Q für o-Phenylen steht, wie es unter (i) in der Definition für Q angegeben ist;

- (b) einem Oxazol, worin X für Sauerstoff und Q für cis-Vinyle steht, wie es unter (ii) in der Definition für Q angegeben ist;
- (c) einem Benzothiazol, worin X für Schwefel steht und Q für o-Phenylene steht, wie es unter (i) in der Definition für Q angegeben ist; und
- (d) einem Thiazol, worin X für Schwefel steht und Q für cis-Vinylene steht, wie es unter (ii) in der Definition für Q angegeben ist;
- sowie den pharmazeutisch zulässigen Basen-Additionssalzen davon.
7. Verbindungen nach einem der Ansprüche 1, 2, 3, 5 oder 6, worin X für Sauerstoff steht; R<sup>4</sup> für R<sup>5</sup>-S-(O<sub>2</sub>)-NH-CO- oder R<sup>5</sup>-S(O<sub>2</sub>)-NH-CO-NR<sup>6</sup>- steht; L für p-Phenylene steht; A für -CO- steht; und R<sup>6</sup> für 4-Chlorophenyl steht.
8. Verbindungen nach Anspruch 4, worin X für Sauerstoff steht; R<sup>4</sup> für R<sup>5</sup>-S(O<sub>2</sub>)-NH-CO- steht; L für p-Phenylene steht; A für -CO- steht; und R<sup>6</sup> für 4-Chlorophenyl steht.
9. Verbindungen nach Anspruch 1, welche ausgewählt sind aus:
- (i) [4-[(4-Chlorophenyl)sulfonylamino-carbonyl]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazol-2-yl)-carbonyl-2-methylpropyl]-L-prolinamid,
  - (ii) [4-[(4-Chlorophenyl)sulfonylamino-carbonyl]benzoyl]-L-valyl-N-[1-[5-(aminocarbonyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamid und
  - (iii) [4-[(4-Chlorophenyl)sulfonylamino-carbonyl]benzoyl]-L-valyl-N-[1-[5-(hydroxymethyl)benzoxazol-2-yl]carbonyl-2-methylpropyl]-L-prolinamid;
- sowie den pharmazeutisch zulässigen Basen-Additionssalzen davon.
10. Salz nach Anspruch 1, welches mit einer ein physiologisch zulässiges Kation bildenden Base hergestellt ist.
11. Verbindungen der Formel III



worin R<sup>4</sup>, L, A, Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, so wie die Salze davon.

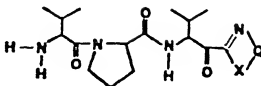
12. Verbindungen der Formel IV



worin R<sup>7</sup> ausgewählt ist aus Carboxy, H<sub>2</sub>N.S(O<sub>2</sub>)-, HNR<sup>8</sup>- und -NCO und R<sup>8</sup> L, A, Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.

13. Verbindungen der Formel V

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(V)

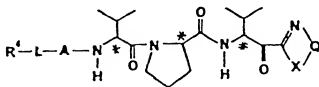
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worin X und Q die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.

14. Pharmazeutische Zusammensetzung, welche eine Leukocytinelastase inhibierende Menge einer Verbindung der Formel I oder eines pharmazeutisch zulässigen Salzes davon sowie ein pharmazeutisch zulässiges Verdünnungs- oder Trägermittel enthält.

15. Verfahren zur Herstellung einer Verbindung der Formel I

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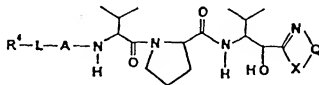
(I)

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oder eines pharmazeutisch zulässigen Salzes davon, wie sie in einem der Ansprüche 1 bis 10 beschrieben sind, dadurch gekennzeichnet, daß man

- (A) für eine Verbindung der Formel I, einen entsprechenden Alkohol der Formel III

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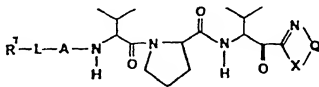
(III)

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oxidiert;

- (B) für eine Verbindung der Formel I, worin R<sup>4</sup> für R<sup>5</sup>.S(O<sub>2</sub>).NH.CO- steht, eine entsprechende Verbindung der Formel IV

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(IV)

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worin R<sup>7</sup> für Carboxy steht, (welche Verbindung nachstehend als "Säure der Formel IV" bezeichnet wird) mit einem Sulfonamid-Derivat der Formel R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> in Gegenwart eines Dehydratisierungsmittels umsetzt oder ein reaktives Derivat einer Säure der Formel IV mit einem Sulfonamid der Formel R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> oder einem Salz davon umsetzt;

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(B-1) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO-$  steht, ein reaktives Derivat einer Säure der Formel IV mit einem Alkalimetallsalz eines ausgewählten Sulfonamids der Formel  $R^5.SO_2.NH_2$  in einem geeigneten Lösungs- oder Verdünnungsmittel umsetzt;

(C) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.CO.NH.S(O_2)-$  steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $H_2N.S(O_2)-$  steht, mit einer Säure der Formel  $R^5.COOH$  umsetzt;

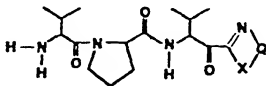
(D) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.NH.CO.NH.S(O_2)-$  steht, eine entsprechende Verbindung der Formel IV worin  $R^7$  für  $H_2N.S(O_2)-$  steht, mit einem Isocyanat der Formel  $R^5.NCO$  umsetzt;

(E) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO.NR^6-$  steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $HNR^6-$  steht, mit einem Sulfonylisocyanat der Formel  $R^5.S(O_2).NCO$  umsetzt;

(E-1) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO.NR^6-$  steht, worin  $R^6$  Wasserstoff bedeutet, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $-NCO$  steht, mit einem Sulfonamid der Formel  $R^5.S(O_2).NH_2$  umsetzt;

(F) für eine Verbindung der Formel I, worin  $R^4$  für  $CF_3.S(O_2).NH-$  steht, ein entsprechendes Amin der Formel IV, worin  $R^7$  für  $H_2N-$  steht, mit Trifluoromethansulfonsäureanhydrid umsetzt;

(G) für eine Verbindung der Formel I, worin A für  $-CO-$  steht, eine Säure der Formel  $R^4-L-COOH$  (oder ein reaktives Derivat davon) mit einem Aminoketon der Formel V

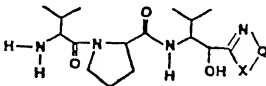


(V)

umsetzt;

worauf, wenn ein pharmazeutisch zulässiges Salz gewünscht wird, eine saure Form der Verbindung der Formel I mit einer Base umgesetzt wird, die ein physiologisch zulässiges Kation liefert.

#### 16. Verbindungen der Formel XV

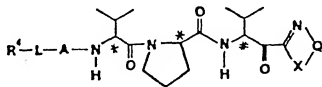


(XV)

worin Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.

#### Patentansprüche für folgenden Vertragsstaat : ES

##### 1. Verfahren zur Herstellung einer Verbindung der Formel I



(I)

worin:

Q ausgewählt ist aus

(i) ortho-Phylen, das gegebenenfalls einen oder zwei Substituenten trägt, die unabhängig ausgewählt sind aus Halogeno, Nitro, Amino-Gruppen der Formel  $-NR^aR^b$ , Acylamino-Gruppen der Formel  $-NHCOR^a$ , Hydroxy, Acyloxy-Gruppen der Formel  $-OCOR^a$ , (1-4C)Alkoxy, (1-4C)Alkyl, Trifluoromethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl, Aminocarbonyl-Gruppen der Formel  $-CONR^aR^b$  - (einschließlich der Formel  $-CONR^aR^b$ , wenn  $R^a=R^b$ ), Sulfo, Sulfonamido-Gruppen der Formel  $-SO_2NR^aR^b$  und (1-3C)Hydroxyalkyl; und

(ii) cis-Vinylen-Gruppen der Formel  $-C(R^a)=C(R^b)-$ ;

$R^a$  und  $R^b$  unabhängig ausgewählt sind aus Wasserstoff, Nitro, Amino-Gruppen der Formel  $-NR^aR^b$ , Acyloxy-Gruppen der Formel  $-OCOR^a$ , (1-4C)Alkoxy, (1-6C)Alkyl, Trifluoromethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl, Aminocarbonyl-Gruppen der Formel  $-CONR^aR^b$  (einschließlich der Formel  $-CONR^aR^b$ , wenn  $R^a=R^b$ ), Hydroxymethyl und Phenyl, das gegebenenfalls einen oder zwei Substituenten trägt, die ausgewählt sind aus Halogeno, Nitro, (1-4C)Alkoxy, (1-4C)Alkyl und Trifluoromethyl;

$R^a$ ,  $R^b$ ,  $R^1$ ,  $R^2$ ,  $R^m$ ,  $R^p$  und  $R^q$  jeweils unabhängig ausgewählt sind aus Wasserstoff und (1-4C)Alkyl;  $R^a$  für (1-4C)Alkyl steht;

X ausgewählt ist aus Sauerstoff und Schwefel;

A ausgewählt ist aus  $-CO-$ ,  $-NH.CO-$  und  $-O.CO-$ ;

L ausgewählt ist aus Phenylen, (1-6C)Alkandiyl, (2-6C)Alkendiyl und Phenylen(1-3C)alkyl, das gegebenenfalls im Alkyl-Teil eine Doppelbindung enthält, mit der Maßgabe, daß ein Kohlenstoffatom, das an einer Doppelbindung eines Alkendiyls oder einer fakultativen Doppelbindung eines Phenylenalkyls beteiligt ist, nicht direkt an ein Sauerstoff- oder Stickstoffatom der Gruppe A gebunden ist;

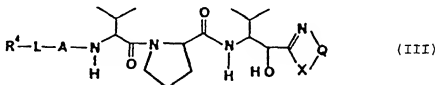
$R^1$  ausgewählt ist aus Acylsulfonamid-Gruppen der Formel  $R^5.S(O_2).NH.CO-$ , Acylsulfonamid-Gruppen der Formel  $R^5.CO.NH.S(O_2)-$ , Sulfonharnstoff-Gruppen der Formel  $R^5.NH.CO.NH.S(O_2)-$ , Sulfonharnstoff-Gruppen der Formel  $R^5.S(O_2).NH.CO.NR^2-$  und Trifluoromethylsulfonamid  $(CF_3.S(O_2).NH)-$ ;

$R^2$  ausgewählt ist aus (1-10C)Alkyl, Trifluoromethyl, (3-10C)Cycloalkyl, (6 und 10C)Aryl, das gegebenenfalls 1 bis 3 Halogeno-, Nitro-, Amino-, Dimethylamino-, Hydroxy-, Methyl-, Trifluoromethyl-, Carboxy-, Phenyl- oder [(1-5C)Alkylcarbonyl]amino-Substituenten trägt, und aromatischen heterocyclischen Gruppen, in denen bis zu 3 Kohlenstoffatome des aromatischen Systems gegebenenfalls unabhängig einen Halogeno- oder Trifluoromethyl-Substituenten tragen; und

$R^2$  für Wasserstoff oder Methyl steht;

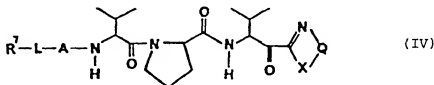
bei welchem Verfahren man

(A) für eine Verbindung der Formel I, einen entsprechenden Alkohol der Formel III



oxidiert;

(B) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO-$  steht, eine entsprechende Verbindung der Formel IV



worin  $R^7$  für Carboxy steht, (welche Verbindung nachstehend als "Säure der Formel IV" bezeichnet wird) mit einem Sulfonamid-Derivat der Formel  $R^5.SO_2.NH_2$  in Gegenwart eine Dehydratisierungsmittels umgesetzt oder ein reaktives Derivat einer Säure der Formel IV mit einem Sulfonamid der

Formel  $R^5 \cdot SO_2 \cdot NH_2$  oder einem Salz davon umsetzt;

(B-1) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5 \cdot S(O_2) \cdot NH \cdot CO-$  steht, ein reaktives Derivat einer Säure der Formel IV mit einem Alkalimetallsalz eines ausgewählten Sulfonamids der Formel  $R^5 \cdot SO_2 \cdot NH_2$  in einem geeigneten Lösungs- oder Verdünnungsmittel umsetzt;

(C) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5 \cdot CO \cdot NH \cdot S(O_2)-$  steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $H_2N \cdot S(O_2)-$  steht, mit einer Säure der Formel  $R^5 \cdot COOH$  umsetzt;

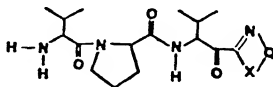
(D) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5 \cdot NH \cdot CO \cdot NH \cdot S(O_2)-$  steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $H_2N \cdot S(O_2)-$  steht, mit einem Isocyanat der Formel  $R^5 \cdot NCO$  umsetzt;

(E) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5 \cdot S(O_2) \cdot NH \cdot CO \cdot NR^6-$  steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $HNR^6-$  steht, mit einem Sulfonylisocyanat der Formel  $R^5 \cdot S(O_2) \cdot NCO$  umsetzt;

(E-1) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5 \cdot S(O_2) \cdot NH \cdot CO \cdot NR^6-$  steht, worin  $R^6$  Wasserstoff bedeutet, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $-NCO$  steht, mit einem Sulfonamid der Formel  $R^5 \cdot S(O_2) \cdot NH_2$  umsetzt;

(F) für eine Verbindung der Formel I, worin  $R^4$  für  $CF_3 \cdot S(O_2) \cdot NH-$  steht, ein entsprechendes Amin der Formel IV, worin  $R^7$  für  $H_2N-$  steht, mit Trifluormethansulfonsäureanhydrid umsetzt;

(G) für eine Verbindung der Formel I, worin A für  $-CO-$  steht, eine Säure der Formel  $R^4-L-COOH$  (oder ein reaktives Derivat davon) mit einem Aminoketon der Formel V



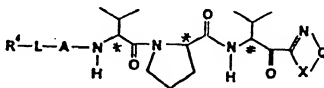
(V)

umsetzt;

worauf, wenn ein pharmazeutisch zulässiges Salz gewünscht wird, eine saure Form der Verbindung der Formel I mit einer Base umgesetzt wird, die ein physiologisch zulässiges Kation liefert.

### 35 Patentansprüche für folgenden Vertragsstaat : GR

#### 1. Verfahren zur Herstellung einer Verbindung der Formel I



(I)

worin:

Q ausgewählt ist aus

(i) ortho-Phenylen, das gegebenenfalls einen oder zwei Substituenten trägt, die unabhängig ausgewählt sind aus Halogeno, Nitro, Amino-Gruppen der Formel  $-NR^aR^b$ , Acylamino-Gruppen der Formel  $-NHCOR^a$ , Hydroxy, Acyloxy-Gruppen der Formel  $-OCOR^a$ , (1-4C)Alkoxy, (1-4C)Alkyl, Trifluormethyl, Carboxy, Cyano, [(1-4C)Alkoxy]carbonyl, Aminocarbonyl-Gruppen der Formel  $-CONR^aR^b$  - (einschließlich der Formel  $-CONR^a_2$ , wenn  $R^b = R^a$ ), Sulfo, Sulfonamido-Gruppen der Formel  $-SO_2NR^aR^b$  und (1-3C)Hydroxyalkyl; und

(ii) cis-Vinylen-Gruppen der Formel  $-C(R^a)=C(R^b)-$ ;

$R^a$  und  $R^b$  unabhängig ausgewählt sind aus Wasserstoff, Nitro, Amino-Gruppen der Formel  $-NR^aR^b$ , Acyloxy-Gruppen der Formel  $-OCOR^a$ , (1-4C)Alkoxy, (1-6C)Alkyl, Trifluormethyl, Carboxy, Cyano, [(1-

4C)Alkoxy)carbonyl, Aminocarbonyl-Gruppen der Formel  $-\text{CONR}^p\text{R}^q$  (einschließlich der Formel  $-\text{CONR}^p$ , wenn  $\text{R}^q = \text{R}^p$ ), Hydroxymethyl und Phenyl, das gegebenenfalls einen oder zwei Substituenten trägt, die ausgewählt sind aus Halogeno, Nitro, (1-4C)Alkoxy, (1-4C)Alkyl und Trifluormethyl;  $\text{R}^p, \text{R}^q, \text{R}^i, \text{R}^j, \text{R}^m, \text{R}^n$  und  $\text{R}^q$  jeweils unabhängig ausgewählt sind aus Wasserstoff und (1-4C)Alkyl;  $\text{R}^n$  für (1-4C)Alkyl steht;

X ausgewählt ist aus Sauerstoff und Schwefel;

A ausgewählt ist aus  $-\text{CO}-$ ,  $-\text{NH.CO}-$  und  $-\text{O.CO}-$ ;

L ausgewählt ist aus Phenylen, (1-6C)Alkandiyl, (2-6C)Alkendiyl und Phenylen(1-3C)alkyl, das gegebenenfalls im Alkyl-Teil eine Doppelbindung enthält, mit der Maßgabe, daß ein Kohlenstoffatom, das an einer Doppelbindung eines Alkendiyls oder einer fakultativen Doppelbindung eines Phenylenalkyls beteiligt ist, nicht direkt an ein Sauerstoff- oder Stickstoffatom der Gruppe A gebunden ist;

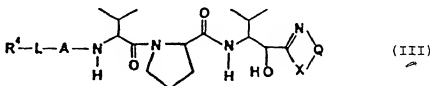
$\text{R}^4$  ausgewählt ist aus Acylsulfonamid-Gruppen der Formel  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$ , Acylsulfonamid-Gruppen der Formel  $\text{R}^5.\text{CO.NH.S}(\text{O}_2)-$ , Sulfonyletharnstoff-Gruppen der Formel  $\text{R}^5.\text{NH.CO.NH.S}(\text{O}_2)-$ , Sulfonyletharnstoff-Gruppen der Formel  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO.NR}^6-$  und Trifluormethylsulfonamid ( $\text{CF}_3.\text{S}(\text{O}_2).\text{NH}-$ );

$\text{R}^5$  ausgewählt ist aus (1-10C)Alkyl, Trifluormethyl, (3-10C)Cycloalkyl, (6 und 10C)Aryl, das gegebenenfalls 1 bis 3 Halogeno-, Nitro-, Amino-, Dimethylamino-, Hydroxy-, Methyl-, Trifluormethyl-, Carboxy-, Phenyl- oder [(1-5C)Alkylcarbonyl]amino-Substituenten trägt, und aromatischen heterocyclischen Gruppen, in denen bis zu 3 Kohlenstoffatome des aromatischen Systems gegebenenfalls unabhängig einen Halogeno- oder Trifluormethyl-Substituenten tragen; und

$\text{R}^6$  für Wasserstoff oder Methyl steht;

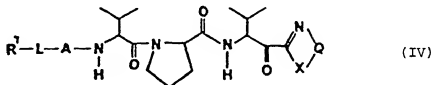
bei welchem Verfahren man

(A) für eine Verbindung der Formel I, einen entsprechenden Alkohol der Formel III



oxidiert;

(B) für eine Verbindung der Formel I, worin  $\text{R}^4$  für  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$  steht, eine entsprechende Verbindung der Formel IV



worin  $\text{R}^7$  für Carboxy steht, (welche Verbindung nachstehend als "Säure der Formel IV" bezeichnet wird) mit einem Sulfonamid-Derivat der Formel  $\text{R}^5.\text{SO}_2.\text{NH}_2$  in Gegenwart eines Dehydratisierungsmittels umsetzt oder ein reaktives Derivat einer Säure der Formel IV mit einem Sulfonamid der Formel  $\text{R}^5.\text{SO}_2.\text{NH}_2$  oder einem Salz davon umsetzt;

(B-1) für eine Verbindung der Formel I, worin  $\text{R}^4$  für  $\text{R}^5.\text{S}(\text{O}_2).\text{NH.CO}-$  steht, ein reaktives Derivat einer Säure der Formel IV mit einem Alkalimetallsalz eines ausgewählten Sulfonamids der Formel  $\text{R}^5.\text{SO}_2.\text{NH}_2$  in einem geeigneten Lösungs- oder Verdünnungsmittel umsetzt;

(C) für eine Verbindung der Formel I, worin  $\text{R}^4$  für  $\text{R}^5.\text{CO.NH.S}(\text{O}_2)-$  steht, eine entsprechende Verbindung der Formel IV, worin  $\text{R}^7$  für  $\text{H}_2\text{N.S}(\text{O}_2)-$  steht, mit einer Säure der Formel  $\text{R}^5.\text{COOH}$  umsetzt;

(D) für eine Verbindung der Formel I, worin  $\text{R}^4$  für  $\text{R}^5.\text{NH.CO.NH.S}(\text{O}_2)-$  steht, eine entsprechende Verbindung der Formel IV worin  $\text{R}^7$  für  $\text{H}_2\text{N.S}(\text{O}_2)-$  steht, mit einem Isocyanat der Formel  $\text{R}^6.\text{NCO}$  umsetzt;

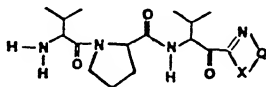


(E) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO.NR^6$ - steht, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $HNR^6$ - steht, mit einem Sulfonylisocyanat der Formel  $R^5.S(O_2).NCO$  umsetzt;

(E-1) für eine Verbindung der Formel I, worin  $R^4$  für  $R^5.S(O_2).NH.CO.NR^6$ - steht, worin  $R^6$  Wasserstoff bedeutet, eine entsprechende Verbindung der Formel IV, worin  $R^7$  für  $-NCO$  steht, mit einem Sulfonamid der Formel  $R^5.S(O_2).NH_2$  umsetzt;

(F) für eine Verbindung der Formel I, worin  $R^4$  für  $CF_3.S(O_2).NH$ - steht, ein entsprechendes Amin der Formel IV, worin  $R^7$  für  $H_2N$ - steht, mit Trifluoromethansulfonsäureanhydrid umsetzt;

(G) für eine Verbindung der Formel I, worin A für  $-CO-$  steht, eine Säure der Formel  $R^4-L-COOH$  (oder ein reaktives Derivat davon) mit einem Aminoketon der Formel V

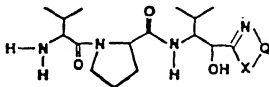


(V)

umsetzt;

worauf, wenn ein pharmazeutisch zulässiges Salz gewünscht wird, eine saure Form der Verbindung der Formel I mit einer Base umgesetzt wird, die ein physiologisch zulässiges Kation liefert.

2. Verbindungen der Formel III von Anspruch 1, worin  $R^4$ , L, A, Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.
3. Verbindungen der Formel IV von Anspruch 1, worin  $R^7$  ausgewählt ist aus Carboxy,  $H_2N.S(O_2)-$ ,  $HNR^6$ - und  $-NCO$  und  $R^6$  L, A, Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.
4. Verbindungen der Formel V von Anspruch 1, worin Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.
5. Verbindungen der Formel XV,



(XV)

worin Q und X die in Anspruch 1 angegebenen Bedeutungen besitzen, sowie die Salze davon.

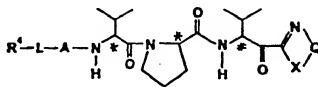
## Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

## 1. Composé de formule I suivante,

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dans laquelle

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le groupe -Q- est choisi entre

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(i) un groupe *ortho*-phénylène, portant facultativement un ou deux substituants choisis, indépendamment, dans un groupe comprenant un substituant halogéno, nitro, un groupe amino de formule -NR<sup>a</sup>R<sup>b</sup>, un groupe acylamino de formule -NHCOR<sup>m</sup>, un groupe hydroxy, un groupe acyloxy de formule -OCOR<sup>n</sup>, alkoxy en C<sub>1</sub> à C<sub>4</sub>, alkyle en C<sub>1</sub> à C<sub>4</sub>, trifluorométhyle, carboxy, cyano, (alkoxy en C<sub>1</sub> à C<sub>4</sub>)carbonyle, un groupe aminocarbonyle de formule -CONR<sup>a</sup>R<sup>b</sup> (y compris la formule -CONR<sup>a</sup> lorsque R<sup>a</sup> est égal à R<sup>b</sup>), sulfo, sulfonamido de formule SO<sub>2</sub>NR<sup>a</sup>R<sup>b</sup> et hydroxyalkyle en C<sub>1</sub> à C<sub>4</sub>; et

(ii) un groupe *cis*-vinylène de formule -C(R<sup>a</sup>)=C(R<sup>b</sup>)- où

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R<sup>a</sup> et R<sup>b</sup> sont tous deux choisis, indépendamment, dans un groupe comprenant l'hydrogène, un groupe nitro, un groupe amino de formule -NR<sup>a</sup>R<sup>b</sup>, un groupe acyloxy de formule -OCOR<sup>n</sup>, un groupe alkoxy en C<sub>1</sub> à C<sub>4</sub>, alkyle en C<sub>1</sub> à C<sub>4</sub>, trifluorométhyle, carboxy, cyano, (alkoxy en C<sub>1</sub> à C<sub>4</sub>)carbonyle, un groupe aminocarbonyle de formule -CONR<sup>a</sup>R<sup>b</sup> (y compris la formule -CONR<sup>a</sup> lorsque R<sup>a</sup> est égal à R<sup>b</sup>), un groupe hydroxyméthyle et un groupe phényle portant facultativement un ou deux substituants choisis entre des substituants halogéno, nitro, alkoxy en C<sub>1</sub> à C<sub>4</sub>, alkyle en C<sub>1</sub> à C<sub>4</sub> et trifluorométhyle ;

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R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, R<sup>e</sup> et R<sup>f</sup> sont choisis chacun, indépendamment, dans un groupe comprenant l'hydrogène et un radical alkyle en C<sub>1</sub> à C<sub>4</sub> ;

R<sup>a</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>4</sub> ;

X est choisi entre l'oxygène et le soufre ;

A est choisi dans un groupe comprenant -CO-, -NH.CO- et -O.CO- ;

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L est choisi entre un groupe phénylène, alcanediyle en C<sub>1</sub> à C<sub>6</sub>, alcènediyle en C<sub>2</sub> à C<sub>6</sub> et phénylène-(alkyle en C<sub>1</sub> à C<sub>3</sub>) contenant facultativement une double liaison dans la partie alkyle, sous réserve qu'un atome de carbone inclus dans une double liaison d'un alcènediyle ou inclus dans une double liaison facultative d'un groupe phénylène-alkyle ne soit pas directement lié à un atome d'oxygène ou d'azote du groupe A ; et

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R<sup>a</sup> est choisi dans un groupe formé d'un acylsulfonamide de formule R<sup>a</sup>.S(O<sub>2</sub>).NH.CO-, d'un acylsulfonamide de formule R<sup>a</sup>.CO.NH.S(O<sub>2</sub>)-, d'une sulfonylurée de formule R<sup>a</sup>.NH.CO.NH.S(O<sub>2</sub>)-, d'une sulfonylurée de formule R<sup>a</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>a</sup>-, et d'un trifluorométhylsulfonamide de formule CF<sub>3</sub>.S(O<sub>2</sub>).NH- où

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R<sup>a</sup> est choisi dans un groupe comprenant un radical alkyle en C<sub>1</sub> à C<sub>10</sub>, trifluorométhyle, cycloalkyle en C<sub>3</sub> à C<sub>10</sub>, aryle en C<sub>6</sub> et C<sub>10</sub> facultativement substitué par 1 à 3 représentants d'un groupe comprenant des substituants halogéno, nitro, amino, diméthylamino, hydroxy, méthyle, trifluorométhyle, carboxy, phényle et [(alkyle en C<sub>1</sub> à C<sub>5</sub>)carbonyl]amino ; et un groupe hétérocyclique aromatique dans lequel jusqu'à 3 atomes de carbone du système aromatique peuvent porter un groupe substituant choisi, indépendamment, entre un radical halogéno et un radical trifluorométhyle ; et

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R<sup>b</sup> est l'hydrogène ou un groupe méthyle ; et

des sels d'addition de bases pharmaceutiquement acceptables de ce composé.

55

2. Composé suivant la revendication 1, dans lequel un substituant facultatif de Q, lorsque Q est un groupe *ortho*-phénylène, est choisi dans le groupe comprenant un radical fluoro, chloro, bromo, nitro, un groupe amino de formule -NR<sup>a</sup>R<sup>b</sup>, un groupe acylamino de formule -NHCOR<sup>m</sup>, hydroxy, un groupe acyloxy de formule -OCOR<sup>n</sup>, méthoxy, éthoxy, propoxy, isopropoxy, tertio-butoxy, méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle, tertio-butyle, trifluorométhyle, carboxy, cyano, méthoxycarbonyle, éthoxycarbonyle, tertio-butoxycarbonyle, un groupe aminocarbonyle de formule -CONR<sup>a</sup>R<sup>b</sup>, un groupe

5 sulfo, un groupe sulfonamido de formule  $\text{SO}_2\text{NR}^i\text{R}^j$ , hydroxyméthyle, 2-hydroxyéthyle et 1,1-diméthylhydroxyméthyle, où  $\text{R}^0$ ,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  et  $\text{R}^7$  sont choisis chacun, indépendamment, dans un groupe comprenant l'hydrogène, les radicaux méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle et tertio-butyle et  $\text{R}^8$  est choisi dans un groupe comprenant les radicaux méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle et tertio-butyle ;  $\text{R}^9$  et  $\text{R}^{10}$  sont tous deux choisis, indépendamment, dans un groupe comprenant l'hydrogène, un groupe nitro, un groupe amino de formule  $-\text{NR}^i\text{R}^j$ , un groupe acyloxy de formule  $-\text{OCOR}^k$ , méthoxy, éthoxy, propoxy, isopropoxy, tertio-butoxy, méthyle, éthyle, propyle, isopropyle, butyle, 2-méthylpropyle, tertio-butyle, trifluorométhyle, carboxy, cyano, méthoxycarbonyle, éthoxycarbonyle, tertio-butoxycarbonyle, un groupe aminocarbonyle de formule  $\text{CONR}^i\text{R}^j$ , un groupe hydroxyméthyle et un groupe phényle portant facultativement un ou deux substituants choisis parmi des substituants fluoro, chloro, bromo, nitro, méthoxy, éthoxy, propoxy, tertio-butoxy, méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle, tertio-butyle et trifluorométhyle,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  et  $\text{R}^4$  étant choisis chacun indépendamment dans un groupe comprenant l'hydrogène et les radicaux méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle et tertio-butyle et  $\text{R}^5$  étant choisi dans un groupe comprenant les radicaux méthyle, éthyle, propyle, isopropyle, 2-méthylpropyle et tertio-butyle ;

15  $\text{R}^6$  est choisi dans un groupe comprenant les radicaux méthyle, éthyle, propyle, isopropyle, tertio-butyle, 4-méthylpentyle, trifluorométhyle, cyclopropyle, cyclopentyle, cyclohexyle, norbornyle, adamantyle, phényle, naphthyle (où un substituant facultatif du noyau phényle ou naphthyle est un substituant fluoro, chloro, bromo, nitro, amino, diméthylamino, hydroxy, méthyle, trifluorométhyle, carboxy, phényle, formylamino, acétylamino, 2-méthylpropanoylamino ou 2,2-diméthylpropanoylamino), un groupe furyle, thiényle, pyridyle et pyrimidinyle portant facultativement sur le groupe hétérocyclique aromatique un substituant fluoro, chloro, bromo ou trifluorométhyle ; et

20 L est choisi entre les groupes p-phénylène, m-phénylène, méthylène, éthane-1,2-diyle, éthane-1,1-diyle, propane-1,3-diyle, propane-1,2-diyle, propène-2,2-diyle, butène-1,4-diyle, 2-méthylpropane-2,3-diyle, 2-méthylpropane-1,2-diyle, pentène-1,5-diyle, éthène-1,2-diyle, propène-1,2-diyle, propène-1,3-diyle, butène-1,4-diyle, but-2-ène-1,4-diyle, pentène-1,5-diyle, 3,3-diméthylpropène-1,3-diyle, p-phénylèneméthyle, 2-[p-phénylène]éthyle, 2-[p-phénylène]-2-propyle et 2-[p-phénylène]éthényle.

3. Composé suivant la revendication 2, dans lequel un substituant facultatif de Q lorsque ce dernier est un groupe o-phénylène est un substituant chloro, diméthylamino, acétylamino, hydroxy, acétoxy, méthoxy, méthyle, trifluorométhyle, carboxy, cyano, méthoxycarbonyle, éthoxycarbonyle, aminocarbonyle, méthylaminocarbonyle, diméthylaminocarbonyle, aminosulfonyle, diméthylaminosulfonyle ou hydroxyméthyle ;

35  $\text{R}^9$  et  $\text{R}^{10}$  sont tous deux choisis, indépendamment, dans un groupe comprenant l'hydrogène, les radicaux diméthylamino, acétoxy, méthoxy, méthyle, trifluorométhyle, cyano, méthoxycarbonyle, aminocarbonyle, méthylaminocarbonyle, diméthylaminocarbonyle, hydroxyméthyle, phényle, chlorophényle, méthoxyphényle et trifluorométhylphényle ;

$\text{R}^1$  est un groupe  $\text{R}^2.\text{S}(\text{O}_2).\text{NH}.\text{CO}-$ ,  $\text{R}^2.\text{S}(\text{O}_2).\text{NH}.\text{CO}.\text{NR}^3-$  ou  $\text{CF}_3.\text{SO}_2.\text{NH}-$  ;

40  $\text{R}^2$  est un choisi dans le groupe comprenant les radicaux méthyle, éthyle, isopropyle, cyclopropyle, cyclopentyle, phényle, chlorophényle, bromophényle, trifluorométhylphényle, 1-naphthyle, 2-thiénylène, 2-pyridyle et chloropyridyle ;

$\text{R}^3$  est l'hydrogène ;

A est un groupe  $-\text{CO}-$  ; et

45 L est un groupe p-phénylène, éthane-1,2-diyle, éthène-1,2-diyle, p-phénylèneméthyle ou 2-[p-phénylène]éthényle.

4. Composé suivant la revendication 3, dans lequel un substituant facultatif porté par Q est un substituant hydroxy, méthoxy, carboxy, méthoxycarbonyle, aminocarbonyle ou hydroxyméthyle ;

$\text{R}^9$  et  $\text{R}^{10}$  sont de l'hydrogène ;

50 L est un groupe méthyle, isopropyle, phényle ou 4-chlorophényle ; et

$\text{R}^2$  est un groupe p-phénylène.

5. Composé suivant la revendication 1, choisi dans un groupe comprenant un benzoxazole dans lequel X est l'oxygène et Q est un groupe ortho-phénylène, un oxazole dans lequel X est l'oxygène et Q est un groupe cis-vinylène de formule  $-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-$ , un benzothiazole dans lequel X est le soufre et Q est un groupe ortho-phénylène, et un thiazole dans lequel X est le soufre et Q est un groupe cis-vinylène de formule  $-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-$  et dans lequel un groupe ortho-phénylène peut facultativement porter un ou deux substituants choisis, indépendamment, dans un groupe comprenant un radical halogéno, un

groupe nitro, un groupe amino de formule  $-NR^aR^b$ , hydroxy, acétoxy, alkoxy en  $C_1$  à  $C_4$ , alkyle en  $C_1$  à  $C_4$ , trifluorométhyle, carboxy, (alkoxy en  $C_1$  à  $C_4$ )carbonyle, sulfo et un groupe sulfonamide de formule  $SO_2NR^aR^b$  ; et dans lequel

$R^a$  et  $R^b$  sont choisis tous deux, indépendamment, dans un groupe comprenant l'hydrogène, un groupe nitro, un groupe amino de formule  $-NR^aR^b$ , alkoxy en  $C_1$  à  $C_4$ , alkyle en  $C_1$  à  $C_4$ , trifluorométhyle, carboxy, cyano, (alkoxy en  $C_1$  à  $C_4$ )carbonyle et un groupe phényle portant facultativement un ou deux substituants choisis dans un groupe comprenant des substituants halogéno, nitro, alkoxy en  $C_1$  à  $C_4$ , alkyle en  $C_1$  à  $C_4$  et trifluorométhyle ;

$R^a$ ,  $R^b$ ,  $R^c$  et  $R^d$  sont choisis chacun, indépendamment, dans un groupe comprenant l'hydrogène et un radical alkyle en  $C_1$  à  $C_4$  ;

A est choisi dans un groupe comprenant  $-CO-$ ,  $-NH.CO-$  et  $-O.CO-$  ;

L est choisi dans un groupe comprenant un radical phénylène, alcanediyle en  $C_1$  à  $C_6$ , alcenediyle en  $C_2$  à  $C_6$ , phénylène-(alkyle en  $C_1$  à  $C_3$ ), contenant facultativement une double liaison dans la partie alkyle, sous réserve qu'une double liaison d'un alcenediyle ou qu'une double liaison facultative d'un groupe phénylène-alkyle ne soit pas en liaison directe avec un atome d'oxygène ou d'azote du groupe A ; et

$R^f$  est choisi dans un groupe comprenant un acylsulfonamide de formule  $R^f.S(O_2).NH.CO-$ , un acylsulfonamide de formule  $R^f.CO.NH.S(O_2)-$ , une sulfonylurée de formule  $R^f.NH.CO.NH.S(O_2)-$  et une sulfonylurée de formule  $R^f.S(O_2).NH.CO.NR^g-$  où

$R^f$  est choisi dans un groupe comprenant un radical alkyle en  $C_1$  à  $C_{10}$ , trifluorométhyle, cycloalkyle en  $C_3$  à  $C_{10}$ , aryle en  $C_6$  et  $C_{12}$  facultativement substitué par 1 à 3 membres choisis dans un groupe formé des substituants halogéno, nitro, amino, diméthylamino, hydroxy, méthyle, trifluorométhyle, carboxy, phényle et [(alkyle en  $C_1$  à  $C_6$ )carbonyl]amino ; et un groupe hétérocyclique aromatique dans lequel jusqu'à 3 des atomes de carbone peuvent porter un groupe substituant choisis, indépendamment, dans un groupe comprenant un radical halogéno et un radical trifluorométhyle ; et

$R^g$  est l'hydrogène ou un groupe méthyle ; et

les sels d'addition de bases pharmaceutiquement acceptables de ce composé.

6. Composé suivant la revendication 1, choisi dans un groupe comprenant :

(a) un benzoxazole dans lequel X est l'oxygène et Q est un groupe o-phénylène tel que défini en (i) dans la définition de Q ;

(b) un oxazole dans lequel X est l'oxygène et Q est un groupe cis-vinylène tel que défini en (ii) dans la définition de Q ;

(c) un benzothiazole dans lequel X est le soufre et Q est un groupe o-phénylène tel que défini en (i) dans la définition de Q ; et

(d) un thiazole dans lequel X est le soufre et Q est un groupe cis-vinylène tel que défini en (ii) dans la définition de Q,

et des sels d'addition de bases pharmaceutiquement acceptables de ce composé.

7. Composé suivant l'une quelconque des revendications 1, 2, 3, 5 ou 6, dans lequel X est l'oxygène ;  $R^a$  est un groupe  $R^f.S(O_2).NH.CO-$  ou  $R^f.S(O_2).NH.CO.NR^g-$  ; L est un groupe p-phénylène ; A est un groupe  $-CO-$  ; et  $R^g$  est un groupe 4-chlorophényle.

8. Composé suivant la revendication 4, dans lequel X est l'oxygène ;  $R^a$  est un groupe  $R^f.S(O_2).NH.CO-$  ; L est un groupe p-phénylène ; A est un groupe  $-CO-$  ; et  $R^g$  est un groupe 4-chlorophényle.

9. Composé suivant la revendication 1, choisi dans le groupe comprenant :

(i) le [4-[(4-chlorophényl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-hydroxybenzoxazole-2-yl)-carbonyl-2-méthylpropyl]-L-prolinamide ;

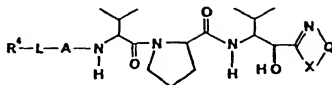
(ii) le [4-[(4-chlorophényl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-(aminocarbonyl)-benzoxazole-2-yl)carbonyl-2-méthylpropyl]-L-prolinamide ; et

(iii) le [4-[(4-chlorophényl)sulfonylaminocarbonyl]benzoyl]-L-valyl-N-[1-(5-hydroxyméthyl)-benzoxazole-2-yl]carbonyl-2-méthylpropyl]-L-prolinamide ;

et ses sels d'addition de bases acceptables du point de vue pharmaceutique.

10. Sel suivant la revendication 1, qui est préparé avec une base formant un cation acceptable du point de vue physiologique.

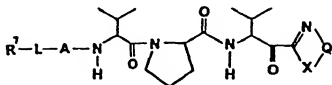
11. Composé de formule III suivante



111

dans laquelle  $R^4$ , L, A, Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.

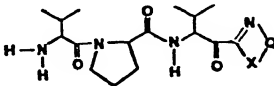
12. Composé de formule IV suivante



IV

dans laquelle  $R^7$  est choisi dans le groupe comprenant un radical carboxy,  $H_2N.S(O_2)-$ ,  $HNR^6-$  et  $-NCO$ , et  $R^6$ , L, A, Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.

13. Composé de formule V suivante

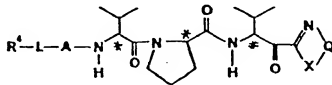


**Y**

dans laquelle Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.

14. Composition pharmaceutique comprenant une quantité inhibitrice d'élastase leucocytaire d'un composé suivant la revendication 1 ou d'un sel pharmaceutiquement acceptable de ce composé et un diluant ou support acceptable du point de vue pharmaceutique.

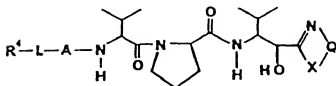
15. Procédé de production d'un composé de formule I suivante



1

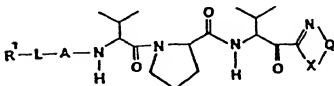
ou d'un sel acceptable du point de vue pharmaceutique de ce composé, suivant l'une quelconque des revendications 1 à 10, qui est caractérisé par :

(A) pour un composé de formule I, l'oxydation d'un alcool correspondant de formule III



III

(B) pour un composé de formule I dans laquelle  $R^4$  représente  $R^5.S(O_2).NH.CO-$ , la réaction d'un composé correspondant de formule IV suivante



IV

dans laquelle  $R^7$  est un groupe carboxy (composé qui sera appelé ci-après "acide de formule IV") avec un dérivé de sulfonamide de formule  $R^5.S(O_2).NH_2$  en présence d'un agent déshydratant ou la réaction d'un dérivé réactif d'un acide de formule IV avec un sulfonamide, ou l'un de ses sels, de formule  $R^5.S(O_2).NH_2$  ;

(B-1) pour un composé de formule I dans laquelle  $R^4$  représente  $R^5.S(O_2).NH.CO-$ , la réaction d'un dérivé réactif d'un acide de formule IV avec un sel de métal alcalin d'un sulfonamide choisi de formule  $R^5.S(O_2).NH_2$  dans un solvant ou diluant convenable ;

(C) pour un composé de formule I dans laquelle  $R^4$  représente  $R^5.CO.NH.S(O_2)-$ , la réaction d'un composé correspondant de formule IV dans laquelle  $R^7$  représente  $H_2N.S(O_2)-$  avec un acide de formule  $R^5.COOH$  ;

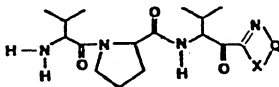
(D) pour un composé de formule I dans laquelle  $R^4$  représente  $R^5.NH.CO.NH.S(O_2)-$ , la réaction d'un composé correspondant de formule IV dans laquelle  $R^7$  représente  $H_2N.S(O_2)-$  avec un isocyanate de formule  $R^5.NCO$  ;

(E) pour un composé de formule I dans laquelle  $R^4$  représente  $R^5.S(O_2).NH.CO.NR^6-$ , la réaction d'un composé correspondant de formule IV dans laquelle  $R^7$  a la valeur  $HNR^6-$  avec un sulfonylisocyanate de formule  $R^5.S(O_2).NCO$  ;

(E-1) pour un composé de formule I dans laquelle  $R^4$  a la valeur  $R^5.S(O_2).NH.CO.NR^6-$ , dans laquelle  $R^6$  est l'hydrogène, la réaction d'un composé correspondant de formule IV dans laquelle  $R^7$  a la valeur  $-NCO$  avec un sulfonamide de formule  $R^5.S(O_2).NH_2$  ;

(F) pour un composé de formule I dans laquelle  $R^4$  a la valeur  $CF_3.S(O_2).NH-$ , la réaction d'une amine correspondante de formule IV dans laquelle  $R^7$  a la valeur  $H_2N-$  avec l'anhydride trifluorométhanesulfonique ;

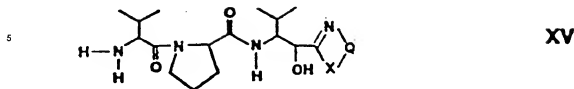
(G) pour un composé de formule I dans laquelle A a la valeur  $-CO-$ , le couplage d'un acide de formule  $R^4-L.COOH$  (ou d'un dérivé réactif de cet acide) avec une aminocétone de formule V



V

après quoi, lorsqu'on désire obtenir un sel acceptable du point de vue pharmaceutique, on fait réagir une forme acide du composé de formule I avec une base pour obtenir un cation acceptable du point de vue physiologique.

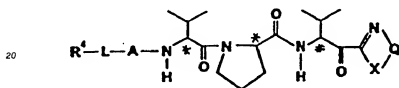
16. Composé de formule XV



<sup>10</sup> dans laquelle Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.

## Revendications pour l'Etat contractant suivant : ES

15 1. Procédé de production d'un composé de formule I suivante



25 dans laquelle :

le groupe -Q- est choisi entre

(i) un groupe ortho-phénylène, portant facultativement un ou deux substituants choisis, indépendamment, dans un groupe comprenant un substituant halogéné, nitro, un groupe amino de formule  $-NR^pR^q$ , un groupe acylamino de formule  $-NHCOR^p$ , un groupe hydroxy, un groupe acyloxy de formule  $-OCOR^p$ , alkoxy en  $C_1$  à  $C_4$ , alkyle en  $C_1$  à  $C_4$ , trifluorométhyle, carboxy, cyano, [alkoxy en  $C_1$  à  $C_4$ ]carbonyl, un groupe aminocarboxyle de formule  $-CONR^pR^q$  (y compris la formule  $-CONR^p_2$  lorsque  $R^p$  est égal à  $R^q$ ), sulfo, sulfonamido de formule  $SO_2NR^pR^q$  et hydroxyalkyle en  $C_1$  à  $C_4$ ; et

(ii) un groupe *cis*-vinylène de formule  $-C(R^1)=C(R^2)-$  où  
 35  $R^1$  et  $R^2$  sont tous deux choisis, indépendamment, dans un groupe comprenant l'hydrogène, un groupe nitro, un groupe amino de formule  $-N(R^3)R^4$ , un groupe acyloxy de formule  $-OCOR^5$ , un groupe alkoxy en  $C_1$  à  $C_6$ , alkyle en  $C_1$  à  $C_6$ , trifluorométhyle, carboxy, cyano, (alkoxy en  $C_1$  à  $C_6$ )carboneyle, un groupe aminocarboneyle de formule  $-CONRR^6$  (y compris la forme  $-CONR^6$  lorsque  $R^6$  est égal à  $R^1$ ), un groupe hydroxyméthyle et un groupe phényle portant facultativement un ou deux substituants  
 40 choisis entre des substituants halogéné, nitro, alkoxy en  $C_1$  à  $C_6$ , alkyle en  $C_1$  à  $C_6$  et trifluorométhyle ;  
 $R^6$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  et  $R^8$  sont choisis chacun, indépendamment, dans un groupe comprenant l'hydrogène et un radical alkyle en  $C_1$  à  $C_6$  ;

R<sup>n</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>4</sub> :

X est choisi entre l'oxygène et le soufre :

45 A est choisi dans un groupe comprenant -CO-, -NH.CO- et -O.CO- ;

L est choisi entre un groupe phénylène, alcanediyle en C<sub>1</sub> à C<sub>6</sub>, alcènediyle en C<sub>2</sub> à C<sub>6</sub> et phénylène-(alkyle en C<sub>1</sub> à C<sub>3</sub>) contenant facultativement une double liaison dans la partie alkyle, sous réserve qu'un atome de carbone inclus dans une double liaison d'un alcènediyle ou inclus dans une double liaison facultative d'un groupe phénylène-alkyle ne soit pas directement lié à un atome d'oxygène ou d'azote du groupe A; et

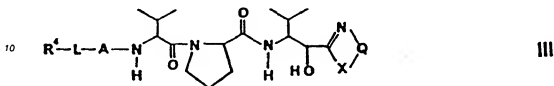
R<sup>4</sup> est choisi dans un groupe formé d'un acylsulfonamide de formule R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, d'un acylsulfonamide de formule R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, d'une sulfonylurée de formule R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, d'une sulfonylurée de formule R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, et d'un trifluorométhylsulfonamide de formule CF<sub>3</sub>.S(O<sub>2</sub>).NH- où

55 R<sup>2</sup> est choisi dans un groupe comprenant un radical alkyle en C<sub>1</sub> à C<sub>10</sub>, trifluorométhyle, cycloalkyle en C<sub>3</sub> à C<sub>10</sub>, aryle en C<sub>6</sub> et C<sub>10</sub> facultativement substitué par 1 à 3 représentants d'un groupe comprenant des substituants halogénés, nitro, amino, diméthylamino, hydroxy, méthyle, trifluorométhyle, carboxy, phényle, et (alkyle en C<sub>1</sub> à C<sub>6</sub>; carbonyl)amino ; et un groupe hétérocyclique

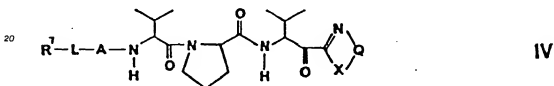
aromatique dans lequel jusqu'à 3 atomes de carbone du système aromatique peuvent porter un groupe substituant choisi, indépendamment, entre un radical halogéno et un radical trifluorométhyle ; et

R<sup>4</sup> est l'hydrogène ou un groupe méthyle ; ledit procédé comprenant un procédé choisi dans un groupe constitué de

(A) pour un composé de formule I, l'oxydation d'un alcool correspondant de formule III



(B) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, la réaction d'un composé correspondant de formule IV suivante



dans laquelle R<sup>7</sup> est un groupe carboxy (composé qui sera appelé ci-après "acide de formule IV") avec un dérivé de sulfonamide de formule R<sup>5</sup>.S(O<sub>2</sub>).NH<sub>2</sub> en présence d'un agent déshydratant ou la réaction d'un dérivé réactif d'un acide de formule IV avec un sulfonamide, ou l'un de ses sels, de formule R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> ;

(B-1) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, la réaction d'un dérivé réactif d'un acide de formule IV avec un sel de métal alcalin d'un sulfonamide choisi de formule R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> dans un solvant ou diluant convenable ;

(C) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> représente H<sub>2</sub>N.S(O<sub>2</sub>)- avec un acide de formule R<sup>5</sup>.COOH ;

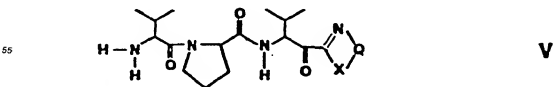
(D) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> représente H<sub>2</sub>N.S(O<sub>2</sub>)- avec un isocyanate de formule R<sup>5</sup>.NCO ;

(E) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> a la valeur HNR<sup>6</sup>- avec un sulfonylisocyanate de formule R<sup>5</sup>.S(O<sub>2</sub>).NCO ;

(E-1) pour un composé de formule I dans laquelle R<sup>4</sup> a la valeur R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, dans laquelle R<sup>6</sup> est l'hydrogène, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> a la valeur -NCO avec un sulfonamide de formule R<sup>5</sup>.S(O<sub>2</sub>).NH<sub>2</sub> ;

(F) pour un composé de formule I dans laquelle R<sup>4</sup> a la valeur CF<sub>3</sub>.S(O<sub>2</sub>).NH-, la réaction d'une amine correspondante de formule IV dans laquelle R<sup>7</sup> a la valeur H<sub>2</sub>N- avec l'anhydride trifluoromethanesulfonique ;

(G) pour un composé de formule I dans laquelle A a la valeur -CO-, le couplage d'un acide de formule R<sup>4</sup>.L-COOH (ou d'un dérivé réactif de cet acide) avec une aminocétone de formule V

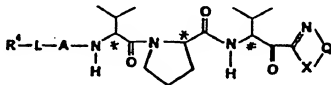




après quoi, lorsqu'on désire obtenir un sel acceptable du point de vue pharmaceutique, on fait réagir une forme acide du composé de formule I avec une base pour obtenir un cation acceptable du point de vue physiologique.

5 Revendications pour l'Etat contractant suivant : GR

1. Procédé de production d'un composé de formule I suivante



dans laquelle :

le groupe -Q- est choisi entre

(i) un groupe ortho-phénylène, portant facultativement un ou deux substituants choisis, indépendamment, dans un groupe comprenant un substituant halogéno, nitro, un groupe amino de formule  $-NR^4R^5$ , un groupe acylamino de formule  $-NHCO-R^6$ , un groupe hydroxy, un groupe alcxylo de formule  $-OCOR^7$ , alkoxy en  $C_1$  à  $C_4$ , alkyle en  $C_1$  à  $C_4$ , trifluorométhyle, carboxy, cyano, [alkoxy en  $C_1$  à  $C_4$ ]carbonyl, un groupe aminocarbonyl de formule  $-CONR^8R^9$  (y compris la formule  $-CONR^2$  lorsque  $R^9$  est égal à  $R^2$ ), sulfo, sulfonamido de formule  $SO_2NR^{10}R^{11}$  et hydroxyalkyle en  $C_1$  à  $C_3$  ; et

(ii) un groupe cis-vinylène de formule  $-C(R^a)=C(R^b)-$  où

R<sup>a</sup> et R<sup>b</sup> sont tous deux choisis, indépendamment, dans un groupe comprenant l'hydrogène, un groupe nitro, un groupe amino de formule -NR<sup>a</sup>R<sup>b</sup>, un groupe alcoxy de formule -OCOR<sup>a</sup>, un groupe alkoxy en C<sub>1</sub> à C<sub>4</sub>, alkyle en C<sub>1</sub> à C<sub>4</sub>, trifluorométhyle, carboxy, cyano, (alkoxy en C<sub>1</sub> à C<sub>4</sub>)carbonyloxy, un groupe aminocarbonyloxy de formule -CONR<sup>a</sup>R<sup>b</sup> (y compris la formule -CONR<sup>a</sup> lorsque R<sup>b</sup> est égal à R<sup>a</sup>), un groupe hydroxyméthyle et un groupe phényle portant facultativement un ou deux substituants choisis entre des substituants halogéno, nitro, alkoxy en C<sub>1</sub> à C<sub>4</sub>, alkyle en C<sub>1</sub> à C<sub>4</sub> et trifluorométhyle ; R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, R<sup>e</sup>, R<sup>f</sup> et R<sup>g</sup> sont choisis, indépendamment, dans un groupe comprenant l'hydrogène et un radical alkyle en C<sub>1</sub> à C<sub>4</sub> ;

R<sup>n</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>4</sub> ;

X est choisi entre l'oxygène et le soufre :

A est choisi dans un groupe comprenant  $-\text{CO}-$ ,  $-\text{NH.CO}-$  et  $-\text{O.CO}-$  :

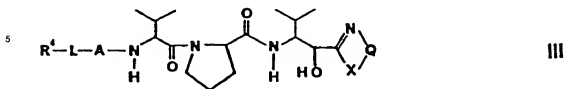
L est choisi entre un groupe phénylène, alcanediyle en C<sub>1</sub> à C<sub>6</sub>, alcènediyle en C<sub>2</sub> à C<sub>6</sub> et phénylène-(alkyle en C<sub>1</sub> à C<sub>3</sub>) contenant facultativement une double liaison dans la partie alkyle, sous réserve qu'un atome de carbone inclus dans une double liaison d'un alcènediyle ou inclus dans une double liaison facultative d'un groupe phénylène-alkyle ne soit pas directement lié à un atome d'oxygène ou d'azote du groupe A; et

R<sup>4</sup> est choisi dans un groupe formé d'un acylsulfonamide de formule R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, d'un acylsulfonamide de formule R<sup>5</sup>.CO.NH.S(O<sub>2</sub>-), d'une sulfonylurée de formule R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>-), d'une sulfonylurée de formule R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, et d'un trifluorométhylsulfonamide de formule CF<sub>3</sub>.S(O<sub>2</sub>).NH- où

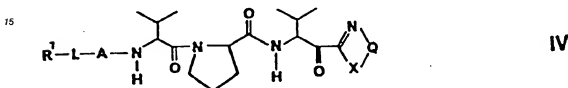
R<sup>2</sup> est choisi dans un groupe comprenant un radical alkyle en C<sub>1</sub> à C<sub>10</sub>, trifluorométhyle, cycloalkyle en C<sub>3</sub> à C<sub>10</sub>, aryle en C<sub>6</sub> et C<sub>10</sub> facultativement substitué par 1 à 3 représentants d'un groupe comprenant des substituants halogéné, nitro, amino, diméthylamino, hydroxy, méthyle, trifluorométhyle, carboxy, phényle, et [alkyle en C<sub>1</sub> à C<sub>5</sub>;carbonyl]amino ; et un groupe hétérocyclique aromatique dans lequel jusqu'à 3 atomes de carbone du système aromatique peuvent porter un groupe substituant choisi, indépendamment, entre un radical halogéné et un radical trifluorométhyle ; et

R<sup>6</sup> est l'hydrogène ou un groupe méthyle ; ledit procédé comprenant un procédé choisi dans un groupe constitué de

(A) pour un composé de formule I, l'oxydation d'un alcool correspondant de formule III



(B) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.SO<sub>2</sub>.NH.CO-, la réaction d'un composé correspondant de formule IV suivante



dans laquelle R<sup>7</sup> est un groupe carboxy (composé qui sera appelé ci-après "acide de formule IV") avec un dérivé de sulfonamide de formule R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> en présence d'un agent déshydratant ou la réaction d'un dérivé réactif d'un acide de formule IV avec un sulfonamide, ou l'un de ses sels, de formule R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> ;

(B-1) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.S(O<sub>2</sub>).NH.CO-, la réaction d'un dérivé réactif d'un acide de formule IV avec un sel de métal alcalin d'un sulfonamide choisi de formule R<sup>5</sup>.SO<sub>2</sub>.NH<sub>2</sub> dans un solvant ou diluant convenable ;

(C) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.CO.NH.S(O<sub>2</sub>)-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> représente H<sub>2</sub>N.S(O<sub>2</sub>)- avec un acide de formule R<sup>5</sup>.COOH ;

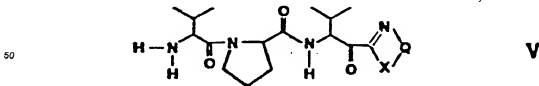
(D) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.NH.CO.NH.S(O<sub>2</sub>)-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> représente H<sub>2</sub>N.S(O<sub>2</sub>)- avec un isocyanate de formule R<sup>5</sup>.NCO ;

(E) pour un composé de formule I dans laquelle R<sup>4</sup> représente R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> a la valeur HNR<sup>6</sup>- avec un sulfonylisocyanate de formule R<sup>5</sup>.S(O<sub>2</sub>).NCO ;

(E-1) pour un composé de formule I dans laquelle R<sup>4</sup> a la valeur R<sup>5</sup>.S(O<sub>2</sub>).NH.CO.NR<sup>6</sup>-, dans laquelle R<sup>6</sup> est l'hydrogène, la réaction d'un composé correspondant de formule IV dans laquelle R<sup>7</sup> a la valeur -NCO avec un sulfonamide de formule R<sup>5</sup>.S(O<sub>2</sub>).NH<sub>2</sub> ;

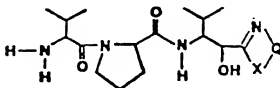
(F) pour un composé de formule I dans laquelle R<sup>4</sup> a la valeur CF<sub>3</sub>.S(O<sub>2</sub>).NH-, la réaction d'une amine correspondante de formule IV dans laquelle R<sup>7</sup> a la valeur H<sub>2</sub>N- avec l'anhydride trifluorométhanesulfonique ;

(G) pour un composé de formule I dans laquelle A a la valeur -CO-, le couplage d'un acide de formule R<sup>4</sup>-L-COOH (ou d'un dérivé réactif de cet acide) avec une aminocétone de formule V



après quoi, lorsqu'on désire obtenir un sel acceptable du point de vue pharmaceutique, on fait réagir une forme acide du composé de formule I avec une base pour obtenir un cation acceptable du point de vue physiologique.

2. Composé de formule III suivant la revendication 1, dans lequel  $R^4$ , L, A, Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.
3. Composé de formule IV suivant la revendication 1, dans lequel  $R^7$  est choisi dans un groupe comprenant les radicaux carboxy,  $H_2N.S(O_2)-$ ,  $HNR^5-$  et  $-NCO$ , et  $R^6$ , L, A, Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.
4. Composé de formule V suivant la revendication 1, dans lequel Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.
5. Composé de formule XV



XV

dans laquelle Q et X sont tels que définis dans la revendication 1, ou un sel de ce composé.